DISEASES of the CHEST

VOLUME XXXVII FEBRUARY, 1960 NUMBER 2

Primary Fibrosarcoma of the Bronchus

PAUL H. HOLINGER, M.D., F.C.C.P.,* KENNETH C. JOHNSTON, M.D., F.C.C.P.,*
NICHOLAS GOSSWEILER, M.D.,** EDWIN C. HIRSCH, M.D.†

Chicago, Illinois

While the incidence of bronchogenic carcinoma is steadily increasing, primary bronchial sarcoma remains an extremely rare disease. Melville, as reported by Drewes,[11] even goes so far as to deny its existence. According to Drewes, primary sarcoma of the bronchi was first described by Poisson and Robbin in 1856. In 1902 Hofman[14] in a review of the entity considered only 23 cases authentic and made the statement that primary sarcoma of the lung is chiefly a disease of the male. This contrasts Noehren's[23] report of an equal sex distribution in the previous literature. He also stated at the beginning of the century that primary sarcoma of the lung was as common a disease as carcinoma. In 1912 Wuest[31] states, Boschowski published statistics of 63 cases and added a new case of his own.

Fuchs in 1886, as reported by Drewes[11] indicated the incidehce of sarcoma in relation to carcinoma as one to seven. This proportion is not in keeping with present interpretation. According to Drewes primary sarcoma of the lung is 100-200 times less frequent than carcinoma. In the Duesseldorfer Clinic two cases of primary sarcoma of the lung were diagnosed in a period of three years whereas five hundred cases of bronchogenic carcinoma were seen during the same period. The Ochsner Clinics[24] recorded seven sarcomas of the lung against 890 cases of bronchogenic carcinoma for the same period. In the review of 8,000 autopsies at the Massachusettes General Hospital, Mallory[20] found one primary sarcoma. Noehren and McKee[22] found one sarcoma in 7,272 autopsies in Kansas City Hospital. Among 11,626 patients who had undergone bronchoscopy at the Mayo Clinic in the years 1945 to 1956, Donohue and Andersen[10] listed only one primary fibrosarcoma of the bronchus.

Sarcoma of the lung seems rather uncommon in very old or very young individuals. Noehren[23] in a survey of 35 cases found the highest incidence in patients in their twenties and the second highest rate of occurrence in patients between fifty to sixty years of age. Only one of his patients was less than ten years old. According to Stout[28] who has made the most thorough recent survey of this condition, fibrosarcoma

*From the Department of Otolaryngology, The University of Illinois, School of Medicine, and the Departments of Bronchoesophagology, Presbyterian — St. Luke's Hospital, and The Children's Memorial Hospital.
**Berne, Switzerland.
†Department of Pathology, Presbyterian — St. Luke's Hospital.

appears to be a disease of young people between the ages of 20 to 29 years. These various statistical findings indicate the extreme rarity of all types of primary sarcomas of the lung. The older statistics might lack some accuracy and Boyd[3] suggests that many of the supposed cases that have been described, undoubtedly were examples of the anaplastic form of carcinoma in which the cells are round, spindle-shaped or oat-shaped. As early as in 1931 Fisher[12] stated that histological interpretation of sarcoma was unsatisfactory and had to be revised. According to this author, the differential diagnosis of so-called primary round-cell sarcoma and of oat-cell tumors of the bronchus lacked accurary. This confusion is especially apparent in the question of diagnosis of fibrosarcoma. Morphologically, fibrosarcomas are described as spindle-cell sarcoma or polymorph-cell sarcoma.[11] However, this more descriptive type of diagnosis is unsatisfactory, insofar as it does not clarify the nature of the tumor. Stout[25] in 1949, has done much to correct the interpretation of the confused subject of fibrosarcoma, having set down clear criteria for evaluating this tumor. Later in 1950, Stout and Himady[27] demonstrated that many solitary tumors, previously reported as fibrosarcoma, leiomysarcoma, etc., had to be considered in another group as mesotheliomas.

Applying the principles suggested by Stout in a review of the literature, Black[1] found five authenticated cases of primary fibrosarcoma of the bronchus and reported one case of his own. The youngest case reported was one by Mallory[21] of a 13-year old girl. The case of another child, a 14-year old boy, was reported by Lewis.[19] We agree with Wuest[31] that the case reported by Curry and Fuchs,[7] a 13-year-old who coughed out a sarcoma of the bronchus, should be added to the other cases previously mentioned. In 1956, an additional case of primary fibrosarcoma of the bronchus in a five and one half year old girl was reported by Donohue, and Andersen[10]. The review of the literature shows us that up to the present time eight cases of clearly diagnosed primary fibrosarcoma of the bronchus have been published. Among these, only four were less than 15 years old; three were girls and one a 14-year old boy.

Case 1: (Lewis)[19] A 14 year old white boy. The tumor was removed bronchoscopically and this was followed by radio-therapy. Two and one-half years after therapy, the patient was reported to be free of disease.[1]

Case 2: (Mallory)[20] A 13-year old white girl. A pulmonary resection was performed but the patient died of intrabronchial hemorrhage.

Case 3: (Curry and Fuchs)[7] A 13-year old white girl. The patient coughed out the tumor and has remained symptomless for four years since this episode. She has had no x-ray film or other therapy.

Case 4: (Donohue and Anderson)[10] A five and one half year old white girl. The tumor was removed through a right thoracotomy. After an uneventful recovery she was followed for three months, but since that time has been lost to routine follow-up. This is the only case of a successfully performed thoracotomy in this type of tumor other than the case herein reported.

Case Report

C. S., a five and one half year old white boy entered St. Luke's Hospital on February 15, 1958. He had a first febrile episode seven months previously which was thought to be due to a middle ear infection. This infection was successfully treated with penicillin. Although he had had a slight cough and fever, he had had no hemoptysis or chest pain, and therefore, no x-ray film examination of the chest had been made.

The second febrile episode occurred in December, 1957. This was more severe and he was hospitalized elsewhere. His temperature rose to 104°F.; wet rales were heard over the right lung, he had a slightly productive cough with blood-tinged sputum once or twice, and pain over the right chest. He had no dyspnea. X-ray film examination showed an atelectasis of the lower portion of the right lung and bronchoscopy demonstrated a tumor in the right bronchus which on biopsy proved to be granulation tissue. Under antibiotic therapy he improved quickly but because of a recurrence of cough and pulmonary symptoms, he was referred for further bronchoscopic studies. On admission he had a persistent cough, productive of a slight amount of yellowish sputum. He had had no hemoptysis, chest pain, dyspnea or fever since the previous hospitalization elsewhere, and had gained in weight. There was no shoulder pain,

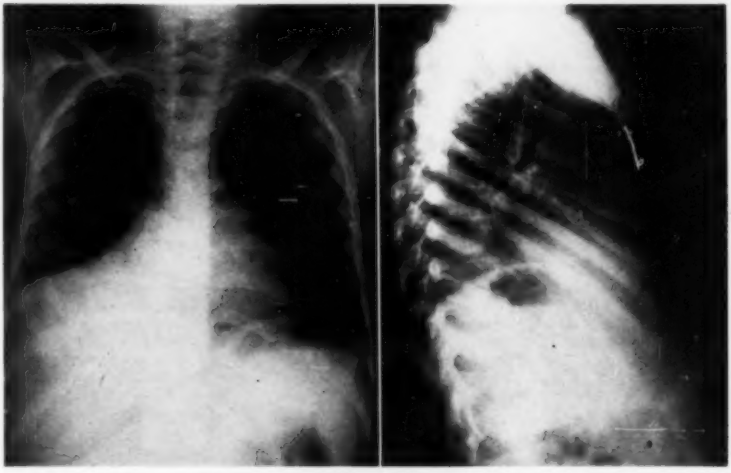


FIGURE 1

FIGURE 1. Admission anterior-posterior and right lateral chest x-ray film showing atelectasis of the right lower lobe subsequently found to be due to fibrosarcoma of the bronchus.

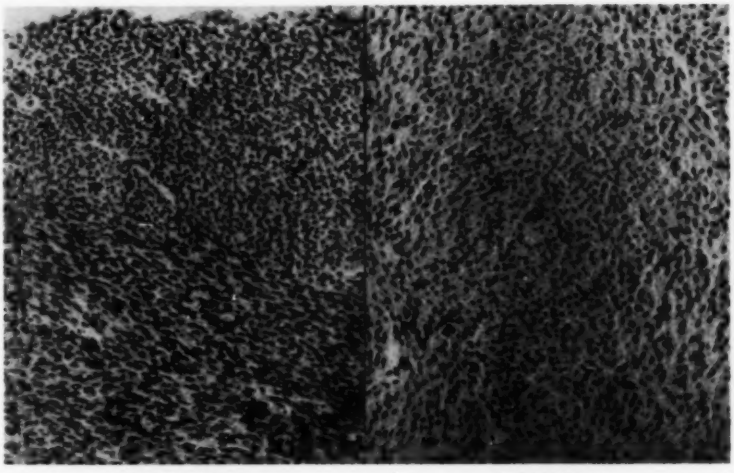


FIGURE 2A FIGURE 2B

FIGURE 2A and B. Photomicrographs illustrating spindle cell structure of the sarcoma of the bronchus.

neuralgia or arthalgia. The family history was non-contributory. He had had measles, mumps, chicken pox, and frequent throat infections. The physical examination revealed a well developed boy in good nutritional state, weighing 44¾ pounds. His temperature was 98.°F. There was decreased fremitus and flatness to percussion with absent breath sounds over the surface projection of the right lower lobe. There were no rales. The antero-posterior and right lateral chest x-ray film showed a homogeneous shadow of increased density corresponding to the right lower lobe. (Fig. 1.) The right leaf of the diaphragm was obliterated and could not be delineated from the collapsed right lower lobe. No significant narrowing of the interspaces was noted and there was no appreciable shift of the mediastinum. The trachea was in the midline. The laboratory examinations were non-contributory.

Bronchoscopic examination showed the right bronchus to be completely obstructed at the level of the middle lobe bronchus by a firm, almost fibrous mass which was round, smooth and unusually tough. The mass was grasped but could not be removed. Small pieces of tissues were obtained for histologic examination and large quantities of very thick, gelatinous sanguinopurulent material was released from below the obstruction and was aspirated. The biopsy showed the obstruction to be due to a fibrosarcoma. (Fig. 2) On surgical exploration by Drs. Van Hazel and Jensik, the right lower and middle lobes were found to be airless, shrunken in size and firm in consistency; the only aereated portion of the lung was the right upper lobe. The lower and middle lobes were excised. It was seen that the tumor was polypoid and had its origin in the right lower lobe bronchus, more posteriorly; the tumor ascended in the bronchus on its pedicle sufficiently to involve the middle lobe, necessitating its removal with the lower lobe. The gross pathology was that of an atelectatic middle and lower lobe. The air passage to as high as the middle lobe had a granular tissue, some of it finely nodular, 1 cm. in diameter, largely filling the channel. The air passages beyond were widely dilated and filled with mucopurulent exudate. The histologic preparations show markedly cellular mesoblastic tissues composed of elongated, spindle-shaped cells and others which are angulated. Many of them are arranged in bands. The cells have fibrillar processes, elongated, vesicular nuclei with chromatin granules and among them some in mitosis. A few large cell forms are in the tissue. The mediastinal lymph nodes taken during the operation showed no tumor tissue. The post-operative course was uneventful. A very thorough study of the patient failed to detect any other evidence of tumor.

Discussion

The symptoms this child manifested are rather typical of persistent bronchial obstruction, but in no way pathognomonic; the onset of a febrile episode followed by a second one, both responding to penicillin therapy is similar to the history of the cases reported by Curry,[7] Mallory,[20] Lewis,[19] and Donohue.[10] Generally the diagnosis is "flu," as in our case, but rheumatic fever and even arthritis are sometimes considered when pulmonary osteoarthropathy is suggested by joint involvement.[5,12,16] In no case of primary sarcoma of the bronchus reported in the literature was there evidence of myoneuropathia due to cerebellar degeneration or any other involvement of the nervous system, as is frequently seen in primary carcinoma of the bronchus unrelated to metastases.[4] Due to the intra-bronchial localization a persistent cough will probably be a symptom of nearly every case of bronchial fibrosarcoma. Noehren[22] cites cough as the chief complaint in sarcoma of the lung (75 per cent of his cases). In younger children it is very difficult to determine whether the cough is productive or not, as they often swallow their sputum. As in our case, Curry's case had a thick, yellowish sputum. Hemoptysis seems to be rather rare in fibrosarcoma of the bronchus, as it is reported only twice by Black, in the case of Carswell and in our case, apparently before admission to the hospital in December, 1957. In Noehren's statistics, 46 per cent of the pulmonary sarcoma cases reported had hemoptysis, which seems to be less frequent than in pulmonary carcinoma, 51 per cent. This might be explained by the fact that sarcoma is generally slower growing than carcinoma, and that this gives more of a chance of earlier diagnosis before the onset of hemoptysis, which has to be considered as a late symptom in neoplasms (Boucot). Dyspnea was reported by Lewis and Mallory, probably also due to pleuritic pain; it was found by Noehren in 26 per cent of his sarcoma cases. This is rather surprising as one would suspect that an obstruction of a bronchus causes some dyspnea. This is probably due to the location, and, therefore, the amount of lung peripheral to the tumor which is involved. It may also be due to the slow growth of this tumor giving the lungs opportunity to adapt their function to the slowly changing conditions. Fever is the most common symptom (Curry, Lewis, Mallory, Noehren, Donohue). The cause is probably more due to the recurrent pneumonia than to any products of the tumor metabolism. In fact, it seems that some children, at least in the beginning, tolerate the sarcoma well. Our patient even gained weight. Holinger reported fibrosarcoma of the larynx of the child also showing an increase in weight. Primary fibrosarcoma of the bronchus appears to be more prevalent in females. X-ray film findings are not typical. The atelectasis was usually interpreted as chronic pneumonia or virus pneumonia. (Carr and Sarokhan), especially when there was no response to antibiotic therapy. It is not the rule that the trachea and mediastinum are pulled toward the involved side, according to Schinz,

although in the cases of Johnson, Lewis and Mallory, the trachea and heart were shifted to the involved side. The aspect of a slow-growing mass (Davies-Ochsner) is unusual (Noehren). Most often the x-ray film diagnosis of atelectasis, (Johnson) pneumonia (Carr, Sarokhan) or contracted lobe (bronchus) is made.

The final diagnosis should be established by biopsy whenever possible, (Stout) and in the majority of cases, a positive result by bronchoscopy can be expected. (Donohue, Yacoubian). Even in solitary pulmonary nodules (Davis, Peabody), one may obtain positive cytology from the aspirated bronchial secretions. Negative biopsies of suspected intrabronchial tumor should be repeated until there is no doubt about the diagnosis. In the case of Killingworth, the biopsies were positive only after four attempts.

FIGURE 3. Surgical specimen of the right lower lobe showing the sarcoma in the basilar branch bronchi of the right lower lobe.

Laboratory examinations are non-contributory. Negative sputum, cytology or a positive histoplasmin reaction does not exclude malignancy. (Prochaska). This is particularly important in solitary nodules; when every laboratory and bronchoscopic attempt to make a diagnosis fails, an exploratory thoracotomy is indicated. (Davies, Donohue, Johnson, Ochsner). Nevertheless, according to Betzler (Drewes) a final diagnosis is difficult to establish and in this type of sarcoma might be unequivocably confirmed only after an interval of 10 years.

Therapy: X-ray therapy was successful in the case of Lewis. In three cases, reported by Black, endobronchial removal was performed successfully, but this author feels that this is not adequate therapy. Because of the high recurrence rate, 60 per cent (Stout), we agree with Davies that lobectomy is the therapy of choice. Pneumonectomy is generally unnecessary unless the tumor lies high in the main bronchus and irreversible pulmonary damage is found distal to it, since there is rarely lymph-node involvement. Pneumonectomy might be considered when the tumor is anaplastic with many mitoses.

The prognosis depends largely on the nature of the tumor. If it is anaplastic with mitoses, the prognosis might be doubtful. Although as a rule metastasis is through the blood stream, lymph node involvement is known (Stout). In cases in which surgery has been done early, the prognosis is good (Curry, Donohue, Drewes, Wuest). A final diagnosis is difficult to make according to Betzler (Drewes) and it can only be made in sarcoma after 10-year intervals.

SUMMARY

A case of primary fibrosarcoma of the bronchus in a five and one half boy is presented. It is the ninth case reported in the literature and with Donohue's patient, the youngest. The diagnosis was established by bronchoscopic biopsy and the tumor successfully removed by lobectomy of the right lower and right middle lobes of the lung. The incidence, symptomatology, diagnosis, therapy and prognosis of fibrosarcoma of the bronchus are discussed.

RESUMEN

Se presenta el caso de un fibrosarcoma primitivo del bronquio en un niño de cinco años y medio. Es el noveno caso relatado en la literatura médica y es con el de Donohue, el más joven.

El diagnóstico es estableció por la biopsia broncoscópica y — el tumor se extirpó con éxito por lobectomía de los lóbulos inferior y medio derechos. La incidencia, la sintomatología, el diagnóstico, terapéutica y pronóstico del fibrosarcoma bronquial, son objeto de disertación

RESUMÉ

Les auteurs présentent un cas de fibrosarcome bronchique primitif chez un garçon âgé de cinq ans et demi. C'est le neuvième cas rapporté dans la littérature, et avec le malade de Donohue, le plus jeune. Le diagnostic fut établi par biopsie bronchoscopique et la tumeur enlevée d'une façon satisfaisante par lobectomie des lobes inférieur et moyen du poumon droit. La fréquence, la symptomatologie, le diagnostic, le traitement et le pronostic du fibrosarcome bronchique sont discutés.

ZUSAMMENFASSUNG

Beschreibung eines Falles eines primären Fibrosarkoms eines Bronchus bei einem 5½-jährigen Jungen.

Es betrifft den 9. in der Literatur mitgeteilten Fall und mit den Patienten von Donohue den Jüngsten. Die Diagnose ergab sich aus der bronchoskopischen Biopsie, und der Tumor konnte erfolgreich entfernt werden durch Lobektomie des rechten Unter- und Mittel-Lappens der Lunge. Diskussion über Vorkommen, Erscheinungsweise, Therapie und Prognose des Fibrosarkoms des Bronchus.

REFERENCES

1 Black, H.: "Fibrosarcoma of the Bronchus," *J. Thorac. Surg.* 19:123, 1950.

2 Boucot, H. R.: "Hemoptysis in Older Man" Lecture at the Fifth Cong. Internat. Soc. Int. Med., Philadelphia, 1958.

3 Boyd, Wm.: *Surgical Pathology Ed.* 5: W. B. Saunders, Philadelphia, 1942 (p. 47).

4 Brain, R.: "Carcinomatous Myoneuropathies," Lect. Fifth Congr. Internat. Soc. Int. Med., Philadelphia, 1958.

5 Carr, D.: "Primary neoplasms of the Lung," *Dis. Chest,* 17:618, 1950.

6 Carswell, J., and Kraeft, N. H.: "Fibrosarcoma of the Bronchus," *J. Thorac. Surg.* 19:117, 1950.

7 Curry, J. J., and Fuchs, J.: "Expectoration of a Fibrosarcoma," *J. Thorac. Surg.* 19:135, 1950.

8 Davis, E. W.: "Significance of solitary intrapulmonary tumor, *S. Clinic, North Amer.* 30:1707, 1950.

9 Davis, E. W.; Peabody, J. W., Jr., and Katz, S.: "The Solitary Pulmonary Nodule," *J. Thorac. Surg.* 32:728, 1956.

10 Donohue, F. E.; Andersen, H. A., and McDonald, J. B.: "Unusual Bronchial Tumor," *Ann. Otol. Rhin. Laryng.* 65:820, 1956.

11 Drewes, J., and Willmann, K. H.: "Das Primaere Lungensarkom, Langenbecks," *Arch. Dtsch. Z. Chir.* 274:95, 1953.

12 Fischer, W.: "Die Gewaechse der Lunge und des Brustfelles," *Henke-Lubarsch, Handbuch der spez. path. Anat. und Hist.* Bd. III/3:520.

13 Gray, K. H., and Whitesell, F. B., Jr.,: "Primary Fibrosarcoma of the Lung," *S. Clin. North Am.* 30:1185, 1950.

14 Hoffmann, F. A.: "Diseases of the Bronchi, Lungs and Pleura," W. B. Saunders, Philadelphia, 1902.

15 Holinger, P. H.; Slaughter, D. P., and Novak, F. J.: "Unusual Tumor Obstructing the Lower Respiratory Tract of Infants and Children." *Tr. Am. Acad. Opht.* 54:223 1950.

16 Johnson, E. K., and Mangiardi, J. L.: "Primary Leiomyosarcoma treated by pneumonectomy," *Surgery* 32:1010, 1952.

17 Killingworth, W. P., and McReynolds, G. S.: "Leiomyosarcoma in Child," *J. Ped.* 42:466, 1953.

18 Lenk, R.: "Die Roentgendiagnostic Intrathorakaler Tumoren und Ihre Differential Diagnose," *Springer,* Wien 1929.

19 Lewis, J.: "Sarcoma of Bronchus," *Proc. Roy Soc. Med.* 40:119, 1947.

20 Mallory, T. B.: "Cabot Case Nr. 24202," *New England J. Med.* 218:843, 1938.

21 Mallory, T. B.: "Cabot Case Nr. 22441," *New Engl. J. Med.* 215:837, 1936.

22 McBurney, R. P., and Claget, O. J.: "Primary Intrapulmonary Neoplasm Associated with Myasthenia Gravis." *Proc. Staff Meet. Mayo Clinic* 26:345, 1951.

23 Noehren, T. H., and McKee, F. W.: "Sarcoma of the Lung," *Dis. Chest* 25:663, 1954.
24 Ochsner,S., and Ochsner, A.: "Primary Sarcoma of the Lung," *Ochsner Clinic Reports* 3:105, 1957.
25 Prochaska, J.; Fingerland, A., and Mydill, F.: "Intrabronchiales Leimyoma," *Thorexchirugie* 5:17, 1957.
26 Schinz, H. R.; Baensch, W. E.; Friedl, E., and Uehlinger, E.: "Roentgen-Diagnosis, Grune and Straton, New York, 1954.
27 Sarokhan, J., and Morrison, D.A.: "Primary Lymphosarkoma," *Ann. Surg.* 138:140, 1953.
28 Stout, A. P.: "Fibrosarcoma the Malignant Tumor of Fibroblasts," *Cancer* 1:30, 1948.
29 Stout, A. P., and Himadi, G. E.: "Solitary (localized) Mesothelioma of the Pleura," *Ann. Surg.* 133:50, 1951.
30 Watson, W. L., and Anylan, A. J.: "Primary Leiomyosarcoma," *Cancer* 7:250, 1954.
31 Wuest, G.: "Das Primaere Lungensarkom (Ein Kasuistischer Beitrag)," *Zentralbi, Allg. Path.* 90:205, 1953.
32 Yacoubian, H.; Conolly, J. E., and Wylie, R. H.: "Leiomyosarcoma of the Lung," *Ann. Surg.* 147:116, 1958.

Experience with Amphotericin in the Therapy of Histoplasmosis

J. L. YATES, M.D., F.C.C.P.,* M. N. ATAY, M.D.,** H. V. LANGELUTTIG, M.D., F.C.C.P.,† C. A. BRASHER, M.D., F.C.C.P.,†† Mt. Vernon, Missouri and M. L. FURCOLOW, M.D., F.C.C.P.,‡ Kansas City, Kansas

Introduction

The general principles of management found to be of value in pulmonary tuberculosis are useful in the therapy of histoplasmosis.[4,12,16] Good nutrition and modified rest programs are beneficial, but without effective antifungal treatment most patients with serious disease will continue to progress. Rubin, *et al.*, report significant worsening of x-ray findings in 79 per cent of 30 patients with chronic pulmonary histoplasmosis during a three-year period of observation.[13]

Numerous antibiotic and chemotherapeutic agents apparently effective *in vitro* have been found to be unsuitable for clinical use either because of toxicity or due to the low blood and tissue levels achieved.[1,3,4,6,16]

The purpose of this paper is to report our experience with Amphotericin B in the therapy of histoplasmosis. We will not repeat information regarding antifungal agents previously published.[1,3-6,12]

Amphotericin B is a polyene antibiotic of unknown structure produced by a streptomyces originally isolated from a soil sample from along the Orinoco River in South America.[9,10,14,15] The oral and intramuscular routes are inadequate for effective therapy.[12] The antibiotic has negligible antibacterial effect but is a potent broad-spectrum antifungal agent, particularly for the yeast phases of the diphasic pathogenic fungi.[2,3,9,15] At present, it seems to be the most valuable agent available for the therapy of the deep mycoses.[2,12]

Amphotericin B is not an ideal antifungal agent for the following reasons: (1) It must be given by the intravenous route. (2) Therapy must be continued for a period of eight to 16 weeks or longer, but the optimum duration of therapy is unknown. (3) There are significant and troublesome side effects. (4) Patient acceptance is relatively poor because of the route of administration, duration of therapy, and the side effects. (5) It is primarily suppressive and not fungicidal, at least in the presence of large amounts of necrotic debris. (6) It has proved to be capable of producing hypersensitivity states similar to those caused by other antibiotics.

The criteria of the effectiveness of an antifungal agent in histoplasmosis are similar to those used in evaluating the antituberculous agents, namely: (1) Conversion of previously consistently positive sputum, blood, or bone marrow cultures; (2) Improvement of x-ray findings; (3) Disappearance of toxicity due to the infection, such as fever, weight loss, malaise, leukopenia, anemia, etc.; (4) Decrease in titer of the comple-

*Chief of Medicine, Missouri State Sanatorium.
**Resident in Pulmonary Diseases, Missouri State Sanatorium.
†Assistant Chief of Medicine, Missouri State Sanatorium.
††Superintendent and Medical Director, Missouri State Sanatorium.
‡Chief, Kansas City Field Station, CDC., U.S.P.H.C.

ment fixation test; (5) Negative cultures or histological examination of resected tissues; (6) Healing of ulcers or other clinical evidences of improvement, such as disappearance of splenomegaly, hepatomegaly, etc.

Clinical Material

The location of the Missouri State Sanatorium on the edge of a highly endemic area for histoplasmosis has resulted in the building up of a series of more than 120 patients with proved histoplasmosis. The majority

TABLE 1

Diagnosis:	No.	Per Cent
A. Chronic pulmonary, cavitary histoplasmosis	27	90.1
B. Disseminated histoplasmosis	2	6.6
C. Acute benign histoplasmosis	1	3.3

of these have, or have had, active, chronic, progressive histoplasmosis with recurrently positive sputa by culture; grossly abnormal chest x-ray films; and significant symptomatology. Thus, an excellent situation exists for the clinical evaluation of chemotherapeutic agents directed at

TABLE 2

Sex and age distribution among 30 cases:

Male: 28 — 93.4 per cent			Female: 2 — 6.6 per cent		
Age:					
0 - 20 years : 2	31 - 40 years : 5		51 - 60 years : 9		
21 - 30 years : 0	41 - 50 years : 5		61 - 70 years : 9		

histoplasmosis. Previous publications based on studies of relatively ineffectual or toxic drugs serve to illustrate this.[3,5-7,13,16] Since 1955, we have had constantly available in the hospital five to ten patients with active pulmonary histoplasmosis. The data presented in this paper are based on the use of Amphotericin B in the treatment of 29 patients with proved histoplasmosis, and one case strongly suggestive of histoplasmosis. The distribution of patients according to the type of clinical disease will be found in Table I. It should be noted that 27 patients were diagnosed as chronic, pulmonary, cavitary histoplasmosis, two had disseminated histoplasmosis, and one was that of a relatively severe acute benign pulmonary histoplasmosis. One of the disseminated cases is now

TABLE 3

The site of lung involvement by X-ray:

No.	Involvement of lung(s)	Total percentage	Involvement of lobe(s)	No. in each group
7	Unilateral	23	Right upper	6
			Left upper	1
23	Bilateral	77	Upper lobe involvement	15
			Upper & lower lobes	5
			Entire both lungs	3

TABLE 4

Pre-Treatment Diagnosis:

No. of Cases	Sputum and pos. culture	Blood and bone marrow culture	Urine Culture	Surgical and biopsy specimen cultures	Percentage
25	+				83.5
1	+	+			3.3
1	+	+	+ (in 2nd admission		3.3
1				+ cervical lymph node	3.3
1				+ left upper lobe tissue	3.3
1					3.3

in his third course of Amphotericin B, having been admitted once in adrenal insufficiency with proved renal involvement.

Table 2 illustrates the sex and age distribution among these patients. It will be noted that the ratio of men to women is 14 to 1, and all patients are of the white race. The majority are over the age of 50 years. It is significant that the acute benign case and one disseminated case occurred in the teen-age group. The two female patients included were between 31 and 40 years of age. The average for the chronic cavitary group was 53.8 years.

The distributions of lung involvement by x-ray film are shown in Table 3. It is noteworthy that 23 patients show bilateral disease and only seven unilateral. Among those with bilateral disease are included three with diffuse nodular disease of miliary type. The distribution of disease by x-ray film resembles that seen in tuberculosis in that it predominately involves the upper lobes.

As illustrated in Table 4, the pretreatment diagnosis was made in 27 cases by culture of the sputum, in one case by a positive culture of a cervical lymph node, and in one by a positive culture from the resected left upper lobe. In one without positive cultures or positive pathological findings, the diagnosis was strongly suggested by the history of sudden onset of a febrile illness two weeks after exposure at a point source (a long vacant chicken house). The clinical picture, chest x-ray films, skin test, and complement fixation were all positive or highly suggestive of histoplasmosis. Tuberculosis was ruled out by negative gastric cultures and negative tuberculin skin tests.

TABLE 5

Pre-Treatment Histo Skin Test and Complement Fixation:

No. of Cases	Histo skin Test	Complement Fixation 1/8 - 1/256	Percentage
25	+	+	83.5
2	+	−	6.6
2	−	+	6.6
1	−	−	3.3

As diagnostic screening tools, complement fixation, and the histoplasmosis skin test were found quite helpful. As a matter of fact, every patient admitted to the sanatorium undergoes a complement fixation test for histoplasmosis first and then a histoplasmin skin test. Table 5 presents a summary of the relationship of the complement fixation tests to the skin tests in the patients reported here. There were positive complement fixations in 27 cases with titers ranging between 1:8 to as high as 1:256. In two cases the complement fixations were negative on admission. In both instances the histoplasmin skin test was positive. In one case all the laboratory tests were negative initially except for the skin test. Later on the complement fixation converted with a titer of 1:128, and immediately after treatment had subsided to 1:32. As may be seen from Table 5, 90 per cent of the patients reported in this paper showed a positive histoplasmin skin test, and 90 per cent showed positive complement fixation.

An estimate of the pretreatment clinical status of these patients revealed that 20 entered the hospital in fair condition and 10 were considered initially to be in poor condition. The general conditions of the acute benign case and the two disseminated histoplasmosis cases were considered poor initially, and on one admission the condition of a disseminated case was actually critical. These patients seemed to show the most dramatic response to Amphotericin B. In four of the chronic pulmonary histoplasmosis cases, there were one or two associated diseases in addition to histoplasmosis. These conditions increased the gravity of the patient's over-all picture. Only three of the chronic cavitary histoplasmosis cases in poor condition initially did not have a complicating disease. One of them (No. 22) showed extensive involvement of the right lung due to histoplasmosis. Later, right pneumonectomy was necessary

TABLE 6—COMPLICATING DISEASES ASSOCIATED WITH HISTOPLASMOSIS IN TEN CASES WHOSE CLINICAL CONDITIONS CONSIDERED POOR

No. of Cases	Diagnosis	Complications or disease besides histoplasmosis	Post Treatment condition
1	Disseminated	Thrombophlebitis Renal involvement of histo and pre-uremia Adrenal Insufficiency	Good
2	Acute Benign pulmonary	None	Good
1	Chronic cavitary	Pul. TB on Rt. c empyema and bilateral bronchopleural fistula	
		A.S.H.D.	Fair
1	Chronic Cavitary	Cor pulmonale Congestive Failure	Fair
1	Chronic Cavitary	Pul. TB moderately advanced Inactive	Fair
2	Chronic Cavitary	None	Fair
1	Chronic Cavitary	A.S.H.D. c Congestive failure	Expired due to congestive failure
1	Chronic Cavitary	None Very extensive disease Rt. pneumonectomy	Expired due to pneumonia 7 months after surgery

but the patient expired approximately seven months following surgery due to bacterial pneumonia in the remaining lung. Table 6 presents the complicating diseases associated with the histoplasmosis in the 10 patients whose pretreatment condition was considered poor.

Methods of Therapy and Observation

The average dosage of Amphotericin B in our series was 0.75 mgm. per kilogram of body weight per day of treatment, administered in 500 to 1000 cc. of 5 per cent glucose in water intravenously. A course of treatment was usually initiated with daily doses of 15 to 25 mgm. given over a six-hour period and increased by 5 mgm. daily until a desired dose was reached, and then the frequency was decreased to three times a week. Ancillary medications consisted of acetylsalicylic acid, meclizine, chlorpromazine, antihistamines, heparin, and hydrocortisone. The latter two were added to the intravenous infusions when necessary, but were only used in an occasional patient. These medications were usually added in the order listed to control side effects of therapy. The careful administration of these drugs at the proper times frequently determined the patient's acceptance of the complete course of therapy. It was the general aim to give four months of Amphotericin as a desired optimum. However, of the 30 patients reported here, only one received less than six weeks of treatment with intravenous Amphotericin B. Several patients also received oral Amphotericin B, but as it became apparent that this was ineffectual, treatment by this route was discontinued. Only one received the oral drug alone. One received only three weeks of Amphotericin B intravenously before he left the hospital against medical advice. The duration of treatment in the others ranged from six to 22 weeks with a spread of total dosages of from 600 to 3,950 milligrams intravenously.

Preliminary laboratory tests included complete blood count, routine urinalysis, blood urea nitrogen, liver function tests including thymol turbidity, cephalin flocculation, BSP and serum bilirubin, electrolytes such as sodium, potassium, and chlorides, and in some cases phenolsulfonphthalein tests. During therapy these tests excluding the bromsulfonphthalein were repeated every two weeks for the first six weeks and then monthly. The BSP did not change in the first patients treated so it was done only before and after a course of therapy. Because the BUN was elevated quite frequently, it was necessary to repeat it more often. In addition, patient's weight, volume of sputum, major temperature elevation, and general clinical condition were recorded weekly. Early in the study sputum cultures were obtained only once every two weeks. During the past year these tests have been obtained weekly and sometimes more often. Sputum examinations by smear and culture for acid-fast bacilli were run routinely approximately every month. Patients underwent chest x-ray films monthly and planigrams every three months. Three of the chronic cavitary cases also had proved pulmonary tuberculosis. Two of these responded well to the routine antituberculous drugs during or before their treatment with Amphotericin B. The third patient's tuberculosis was apparently arrested, but he suffered a seem-

ing relapse and was readmitted to the hospital. However, the active pulmonary disease at this time was proved to be histoplasmosis by positive sputum culture.

Side Effects

The 29 patients treated with intravenous Amphotericin B experienced varying degrees of side effects as illustrated in Table 7. Side effects did not result from oral administration, even in doses of 8 grams per day. In only three patients were we compelled to discontinue drugs because of untoward side effects. In one the drug was discontinued because of the development of acute polymyositis, believed to be related to hypersensitivity angiitis. After discontinuance of the drug, he made prompt recovery, and the drug has not been restarted since the histoplasmosis continues to regress. One patient's treatment was discontinued because of severe malaise, fever, and headache with even low doses of Amphotericin B. One experienced severe malaise with fever of 102°F every day of therapy in spite of ancillary medications but persisted in treatment for four months and achieved an excellent clinical result. One patient's therapy was discontinued after two months because of the development of purpuric rash limited to the ankles and feet. This patient was also on other therapy including Diuril and digitalis for congestive heart failure, and it is not known for sure which treatment caused his rash. However, it is included as a side effect of Amphotericin because it is not usually seen with these other drugs. Three left the hospital against medical advice, one after three months therapy, another after two months, and the third after only three weeks although this latter's sputum had converted to negative. A few patients developed inflammation around the veins and apparently of the vein itself without developing thromboses secondary to this. This would disappear within 48 to 72 hours without residue. The addition of 25 mgm. of Heparin to the intravenous infusion prevented this complication. A number of patients who suffered systemic reactions received 10 to 25 mgm. of hydrocortisone in each infusion with success in control of the side effects.[13] A patient with disseminated histoplasmosis also received intravenous hydrocortisone and oral methylprednisolone because of the adrenal insufficiency due to histoplasmosis. The usual side effects of chills, fever, headache, and general malaise could be controlled rather well by administering acetylsalicylic acid every two to four hours during therapy, meclizine regularly, and chlorpromazine. The patients also were kept comfortably warm, and they were encouraged to force fluids. Nausea was controlled by meclizine and chlorpromazine. Anorexia and apparently unrelated

TABLE 7

Side effect in 29 cases treated c I.V. Amphotericin B		of symptoms in 23 cases Side effects — relative frequency			
None:	6	Anorexia:	16	Nausea:	7
Mild:	8	Chill:	14	Diarrhea:	2
Moderate:	10	Headache:	9	Rash:	1
Severe:	5	Fever:	9	Pruritis:	1
		Emesis:	7	Polymyositis:	1

nausea were common, and were difficult to control (see Table 7). However, these patients were encouraged to eat and succeeded in maintaining their nutrition fairly well. Indeed the rapport between the patient and physician was an essential part of keeping them on therapy.

In addition to the above symptoms which were really not of too great concern, the major side effect was azotemia. A blood urea nitrogen of more than 20 mgm. per cent occurred in 24 patients sometime during the course of Amphotericin therapy and was frequently associated with hyaline casts in the urine. We also noted a decrease in the PSP excretion in the few on whom this test was done. This has been confirmed by other workers. The BUN usually could be decreased by forcing fluids even during treatment, and the BUN returned to a normal level within two to four weeks after discontinuing the drug. In two patients, Amphotericin B was discontinued because of an elevated BUN, which in one case was 70 mgm. per cent, and in the other near 60 mgm. In most of the patients the BUN remained between 30 and 40 mgm. The patient whose BUN was 70 mgm. and whose drug was discontinued was later re-admitted at the end of seven months and again found to have an elevation of the BUN. This time, however, it was found that two urine cultures were positive for *Histoplasma capsulatum*. However, with treatment directed at adrenal insufficiency, which was also present, and Amphotericin B, his BUN fell to approximately 30 mgm. per cent, and the intravenous pyelograms were found to be normal. There did not appear to be any correlation between the symptomatic side effects and the elevated BUN.

Therapeutic Results

The duration of intravenous Amphotericin B therapy in this series of patients varied between three weeks and five and one half months. More detailed explanation of this and the correlation of the number of patients and their total doses of intravenous Amphotericin B in milligrams may be seen in Table 8. One case (No. 20) is not included since he received oral Amphotericin B alone. The average duration of intravenous therapy was three months, and one case is still under therapy. One case has just begun his third course of intravenous Amphotericin B in conjunction with adreno-steroid therapy and is already showing remarkable clinical improvement. However, his BUN is somewhat elevated.

The results of intravenous Amphotericin B therapy, as evaluated by change in clinical condition, x-ray findings improvement, decreasing amount of sputum, conversion of positive sputum, and changes in titer of complement fixation, are shown in Table 9. A striking feature has

TABLE 8

Total dose of Amphotericin B and duration of treatment (only I.V.)

Duration		Total I.V. Amphotericin B	
3-6 weeks:	4 cases	600-1,000 mg.:	8 cases
7 weeks-2½ months:	8 cases	1100-2,000 mg.:	9 cases
3-5 months:	15 cases	2100 and more:	13 cases
More than 5 months	2 cases		

TABLE 9

Pre and post treatment clinical condition:

No. of cases	Pre-treatment clinical condition	Post-treatment clinical condition
3	Poor	Good
6	Poor	Fair
1	Poor	Poor
3	Fair	Fair
17	Fair	Good

been conversion of sputum cultures to negative usually within the first two or three weeks of therapy with three notable exceptions in which the conversion occurred during the second month of treatment. Sputa were not considered to have converted unless there were a number of consecutive positive specimens which later were consistently negative. One patient who was treated first with the insoluble suspension of Amphotericin B and later with the lyophilized preparation, both times revealed sputum conversion during treatment but promptly reconverted to positive and remained so. Another patient with destruction of one lung and a bronchopleural fistula with empyema and a consistently positive sputum became negative during the second month of treatment and remained so for two and one half months, at which time treatment was discontinued. This patient suffered a clinical and a sputum relapse within two weeks, and he remains consistently positive at this time. He has not benefited from a two months course of intramuscular Amphotericin B.

X-ray film improvement has not been as impressive, particularly in chronic cavitary disease, although remarkable clearing can be shown in the acute benign and both of the disseminated cases. In Table 9 using the above criteria for evaluation, we find that 25 patients showed moderate to marked improvement, five are essentially unchanged. The most dramatic responses were obtained in disseminated and benign cases.

Table 10 illustrates the improvement by x-ray film, and it may be seen that whereas 25 patients showed a moderate to marked clinical improvement, only 13 showed moderate to marked x-ray film improvement. Seventeen showed slight, or temporary improvement, or no change. Three showing marked improvement were of the acute benign and disseminated types of disease. Only two of the chronic cavitary cases showed marked improvement.

The amount of sputum decreased remarkably in all cases while under therapy. In those who discontinued at the end of a short period, such as three to eight weeks, sputum usually increased promptly and their

TABLE 10

Post-treatment X-ray film improvement:

No. of cases	X-ray changes
5	Marked improvement
8	Moderate improvement
12	Slight improvement
1	Temporary
4	No change

clinical symptoms returned especially if they still showed considerable x-ray film findings.

The change of the complement fixation titer could not be predicted. However, the general trend was from higher to lower titers as therapy continued. In two patients positive complement fixation converted to negative during therapy. In one case the only positive complement fixation test occurred during treatment. The complement fixation tests of the remaining patients merely showed decreasing titers.

With reference to sputum results, three patients did not have positive sputum initially. Two of these had shown positive cultures from tissue specimens, one from a lymph node, and the other from a resected lung section. These patients had been treated because of exacerbating disease in the same lung or the opposite lung, which was proved to be nontuberculous by finding negative tuberculin skin tests and many negative sputum cultures from acid-fast bacilli. Twenty-seven patients were positive by sputum culture prior to therapy, and in the majority of them there were repeatedly positive cultures. Four showed less than three positive cultures prior to treatment. The remainder showed three or more positive cultures immediately before treatment. One who had previously had active tuberculosis, now proved to be inactive by many negative sputum cultures over a period of at least a year, showed active progression by x-ray film and then marked improvement under Amphotericin B therapy, in spite of developing active polymyositis after receiving treatment for only six weeks. This patient remains in the hospital and is still showing x-ray film improvement six weeks after discontinuing Amphotericin B. His sputum cultures have remained negative for *Histoplasma capsulatum*. One patient with only one positive sputum culture prior to therapy had developed a cavity in the opposite lung nine months after resection of the upper lobe of the other lung which was shown to be positive by culture for histoplasmosis. The x-ray showed decrease of the reaction around the cavity and thinning of the cavity wall. However, at the end of four months of treatment the cavity remained as a stable cyst-like structure. He refused further surgery but remains clinically well and unchanged by x-ray film two months after cessation of therapy. Another improved on bed rest by x-ray film and clinical findings and then seemed to become stable. He showed further clinical and x-ray film improvement on Amphotericin B therapy but still required resectional surgery because of recurrence of symptoms. Since this surgery was done elsewhere, we are not able to give the results of sputum cultures prior to surgery. The tissue resected revealed a caseous necrotic granuloma but was negative on culture for *Histoplasma capsulatum*. Two years after surgery he remains well, with x-ray film findings stable, and he is leading a normal life. Another who only had one positive from a lymph node was treated prophylactically for two months with apparent x-ray film improvement during treatment but subsequently, 10 months after treatment, an x-ray film showed marked increase in the infiltrative changes in the same lung, and the patient has refused to return for evaluation or therapy. The rest of the patients have shown conversion of sputum by multiple tests during the Amphotericin B therapy.

Follow-Up Information

Complete follow-up is available in 20 cases from 0 to 24 months; two are still in the hospital. One is being treated for the third time with Amphotericin B, and another is the patient who has been mentioned previously as having had six weeks of Amphotericin and then developing polymyositis. Two expired after discharge from the sanatorium. One died from congestive heart failure, and the other who had right pneumonectomy died seven months after surgery due to lobar pneumonia. Two recent patients, who are included in the tables, left the hospital against medical advise, and follow-up is not available as yet. Also, four discharged patients have been lost to follow-up at between one to ten months. The 20 who have been followed carefully by x-ray film from two to 24 months have not all had sputum examinations, but seven of them have, and have remained negative between five and 21 months. More detailed information about x-ray film and sputum follow-up is given below. Seven showed further clearing and stability of x-ray findings over a period of three to 24 months. Ten cases showed no change by x-ray film in two to 21 months follow-up. Two had further increase in infiltration. One whose x-ray film cleared during treatment and remained so was readmitted five months later with renal involvement. In seven followed by sputum studies, three have remained negative from five to 12 months while four reverted back to positive sputum again in five to 21 months. Two illustrative cases with key x-ray films reproduced are included here to further elucidate our results and the problems of therapy of histoplasmosis.

Case 10: This 33 year old white woman had been feeling tired and having slight cough for one year. No history of dyspnea, chest pain, or weight loss. She had a mobile unit x-ray film, and sanatorium care was recommended because of infiltrative lesion in one lung. She entered this sanatorium on October 31, 1957.

Physical examination showed a few crepitant rales throughout both lungs. No other abnormal finding was noted.

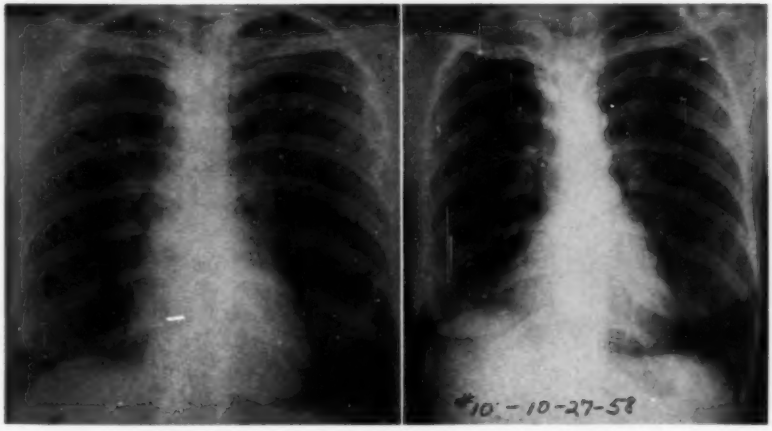


FIGURE 1A FIGURE 1B

FIGURE 1A. (Case No. 10): Chronic, unilateral, cavitary, histoplasmosis in right upper lobe three weeks prior to therapy. FIGURE 1B. Same case nine months after right upper lobectomy. (Surgery was performed while she was on Amphotericin B treatment.)

Laboratory findings: Histoplasmin skin test was positive, and complement fixation was 1:8. The first positive sputum culture was on November 21, 1957, and remained positive up to January 2, 1958, then converted to negative.

Intravenous Amphotericin B was started on December 16, 1957 and continued to January 19, 1958, with total dose of 570 mg. in six weeks. On January 13, 1958 she had right upper lobectomy. Culture from right upper lobe tissue was negative for histoplasmosis. Tissue was positive for yeast bodies with methenamine silver stains, but not on culture.

This patient's condition remains satisfactory, according to correspondence in March, 1959, and the last follow-up x-ray film of February 19, 1959 is stable (Figure 1).

Discussion: This woman is an example of chronic pulmonary histoplasmosis. She was operated after only six weeks of therapy, primarily because her acceptance of the treatment was poor and we believed it best to proceed while her sputum was negative and using the Amphotericin as an umbrella. She received therapy for ten days postoperatively.

Case 26: This 48 year old white man was admitted to this sanatorium on December 9, 1958 with complaints of cough, weakness, and raising sputum. His complaints started five weeks prior to admission, at which time he developed cough and low grade fever. Later on he became quite weak and lost his appetite. He also lost about eight to ten pounds during that time. There was no history of shortness of breath. He was seen by a physician a week ago, who took an x-ray film and advised sanatorium treatment.

Physical examination revealed an active, well developed white man. His blood pressure was 115/70, temperature 98.6. The only abnormal findings were moderately depressed breath tones in both lung fields with crepitant rales in both upper lobes posteriorly. Percussion was impaired in right interscapular region.

Laboratory findings: PPD and histoplasmin skin tests were positive. Complement fixation titer was 1:128. Numerous sputa cultures were negative for acid-fast bacilli. On January 14, 1959 sputum was reported positive for histoplasmosis and remained positive until March 1, 1959.

Course: Intravenous Amphotericin B was started on February 4, 1959, and continued three months, totalling 2060 mg. The sputum converted to negative on March 23, 1959, and since that time four sputum cultures were reported negative, and last complement fixation titer was 1:32. He tolerated the medicine well without side effects. X-ray films showed marked improvement. (See Figure 2).

Discussion: Chronic pulmonary histoplasmosis. Further therapy is deemed advisable, but optimum duration is unknown.

Discussion

As mentioned previously, Amphotericin B is probably the best available therapy for deep mycoses at the present time. However, on the basis of our study, it has shown

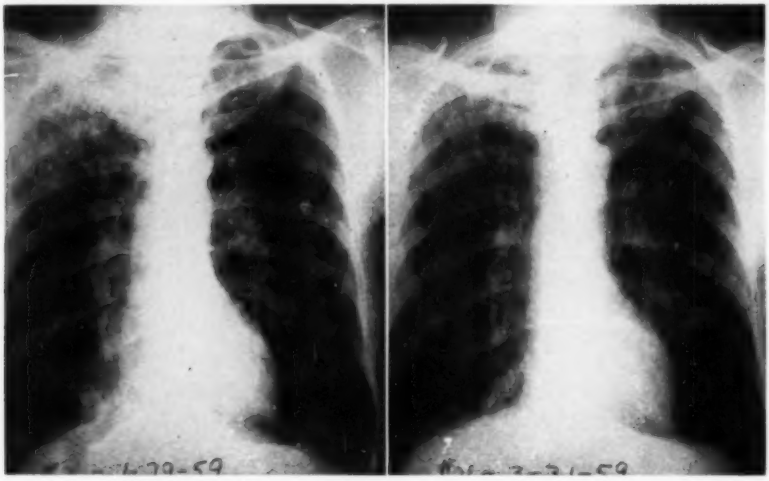


FIGURE 2A FIGURE 2B

FIGURE 2A (Case No. 26): Chronic cavitary bilateral pulmonary histoplasmosis one week prior to therapy. FIGURE 2B. Second month of the intravenous Amphotericin treatment. Considerable clearing in both upper lobes, but more marked on the right side. Decreasing size of cavity is significant.

itself to be primarily suppressive in that it will consistently produce sputum conversion and clinical improvement, but less surely marked x-ray film improvement. This, of course, is not astonishing in view of our experience with streptomycin in tuberculosis. Apparently, as in tuberculosis, when there is a large amount of necrotic disease debris present, it is difficult for the drug to do more than to inhibit the organism and thereby convert the sputum to negative. It will remain for other therapy, such as resectional surgery as well as thoracoplasty, to provide permanent cure in a moderate number of cases. It has been shown by *in vitro* testing that fungi can be made resistant to both nystatin and Amphotericin B.[1] One of our patients with disseminated histoplasmosis, who received four months of therapy as compared to two months originally, relapsed after a relatively shorter time; namely, approximately two months as compared with the original seven months. This suggests an increase in resistance of the organisms. Other studies with regard to resistance are still in process, and insufficient data is available at this time. Several of our cases have shown clinical and sputum relapse when treatment was discontinued while still obviously active by x-ray film but with sputum negative by repeated culture. This, of course, indicates that we must search further to improve the tissue levels that can be achieved with Amphotericin B. We should try to find a way to administer Amphotericin B more effectively so that we will receive greater patient acceptance and will allow treatment over a longer period of time as in the case with antituberculosis therapy. There is a need to develop other antifungal agents which can be administered in conjunction with Amphotericin B, either simultaneously or consecutively, to improve the over-all results.

SUMMARY

We have reported our experience with the use of Amphotericin B therapy in 29 cases of proved active histoplasmosis, and one strongly suspected case. Our results apparently show that the drug is effective, but is primarily suppressive. Although it is the best therapy available now, there is a real need for further study and development of other antifungal agents which can be used in conjunction with Amphotericin and perhaps other methods of administration of the drug should be studied. Also, in view of the toxic effects, the manufacturers should be encouraged to attempt to purify and obtain the active principle in Amphotericin B.

RESUMEN

Hemos referido nuestra experiencia con el uso de la Anfotericina B en 29 casos de histoplasmosis activa demostrada y en un caso fuertemente sospechoso. Nuestros resultados muestran que aparentemente la droga es eficaz, pero en primer lugar es supresora. Aunque es el mejor tratamiento que hay ahora, hay una necesidad verdadera de un estudio ulterior de otros agentes fungicidas que puedan usarse con la Anfotericina y probablemente deban estudiarse otros métodos de administración de la droga. También, en vista de la toxicidad, los fabricantes deben ser alentados para que intenten purificarla y obtener el principio activo de la Anfotericina B.

RESUMÉ

Les auteurs rapportent leur expérience du traitement par l'amphotéricine B dans 29 cas d'histoplasmose évolutive démontrée, et dans un cas fortement suspect. Leurs résultats montrent nettement que le produit est efficace, mais qu'il est essentiellement palliatif. Bien que ce soit le mailleur traitement dont nous disposions actuellement, il y a un réel besoin que l'on étudie d'autres agents antifungiques, pouvant être utilisés en association avec l'amphotéricine, et peutêtre d'autres méthodes d'administration du produit. Pour éliminer les effets toxiques, les fabricants devraient être encouragés à essayer de purifier l'amphotéricine B et d'en obtenir le principe actif.

ZUSAMMENFASSUNG

Wir haben über unsere Erfahrungen berichtet hinsichtlich der Verwendung der Amphotericin B Therapie bei 29 nachgewiesenen und 1 stark verdächtigen Fall von aktiver Histoplasmose. Unsere Ergebnisse zeigen tatsächlich, da dieses Medikament von Wirksamkeit ist, jedoch in erster Linie im Sinne einer Hemmung. Obwohl dies die beste derzeit zur Verfügung stehende Therapie ist, besteht die Notwendigkeit zu weiteren Untersuchungen und der Enwicklung anderer pilzbekämpfender Stoffe, die sich zusammen mit Amphotericin verwend den lassen; auch mülen vielleicht noch andere Methoden des Einsatzes des Medikamentes geprüft werden. Ferner sollte, im Hinblick auf die Toxizität, die Herstellerfirma veranlasst werden, Amphotericin B in reiner Form darzustellen und seinen aktiven Wirkstoff zu gewinnen.

REFERENCES

1 Procknow, J. J., and Loosli, C. G.: "Treatment of the Deep Mycoses," *AMA Arch. Int. Med.* 101:765, 1958.

2 Baum, G. L.; Schwarz, Jan, and Wang, C. J. K.: "Treatment of Experimental Histoplasmosis with Amphotericin B," *AMA Arch. Int. Med.* 101:84, 1958.

3 Lehan, P. H.; Yates, J. L.; Brasher, C. A.; Larsh, H. W., and Furcolow, M. L.: "Experiences with the Therapy of Sixty Cases of Deep Mycotic Infection," *Dis. of Chest* 32:597, 1957.

4 Silverman, F. N.; Schwarz, Jan; Lahey, M. E., and Carson, R. P.: "Histoplasmosis," *Am. J. Med.* 19:410, 1955.

5 Brasher, C. A., and Furcolow, M. L.: "Problems in Treatment of Chronic Histoplasmosis as Experienced in over 20 Cases," p. 287, *Therapy of Fungus Diseases*, Steinberg and Newcomer; Little, Brown & Co., 1955.

6 Lehan, P. H.; Furcolow, M. L.; Brasher, C. A., and Larsh, H. W.: "Therapeutic Trials with Newer Antifungal Agents," *Antibiotics Annual* 1956-57, p. 462 (Medical Encyclopedia, Inc.)

7 Furcolow, M. L., and Brasher, C. A.: "Chronic Progressive (Cavitary) Histoplasmosis as a Problem in Tb. Sanatoria," *Am. Rev. Tb. and Pulm Dis.* 73:609, 1956.

8 Curry, F. J., and Weir, J. A.: "Histoplasmosis (A Review of 100 Consecutively Hospitalized Patients)," *Am. Rev. of Tb. and Pulm. Dis.* 77:749, 1958.

9 Louria, D. B.; Feder, N., and Emmons, C. W.: "Amphotericin B in Experimental Histoplasmosis and Cryptococococsis," *Antibiotics Annual*, 1956-57, p. 866.

10 Utz, J. P.; Louria, D. B.; Feder, N.; Emmons, C. W., and McCullough, N. B.: "A Report of Clinical Studies on the Use of Amphotericin in Patients with Systemic Fungal Diseases," *Antibiotics Annual* 1957-58, p. 53.

11 Littman, M. L.; Pisano, M. A., and Lancaster, R. M.: "Induced Resistance of Candida Species to Nystatin and Amphotericin B," *Antibiotics Annual* 1957-58, p. 981.

12 Seabury, J. N., and Doscomb: "Experience with Amphotericin B for the Treatment of Systemic Mycoses," *AMA Arch. Int. Med.* 102:960, 1958.

13 Rubin, H.; Furcolow, M. L.; Brasher, C. A., and Yates, J. L.: "The Course and Prognosis of Histoplasmosis," *Amer. J. Med.* 27:278, 1959.

14 Vogel, R. A., and Crutcher, J. D.: "Studies on the Bio-assay and Excretion of Amphotericin B in Patients with Systemic Mycoses," *Antibiotic Medicine and Clinical Therapy* 5:501, 1958.

15 Sternberg, T. H.; Wright, E. T., and Oura, M.: "A New Antifungal Antibiotic, Amphotericin B," *Antibiotics Annual* 1955-56, p. 566.

16 Yates, J. L.; Langeluttig, H. V., and Brasher, C. A.: Chapter, "Medical Management of Histoplasmosis," in book edited by Henry C. Sweany, M.D., Charles C. Thomas, Publisher, in press.

Lipoid Pneumonia Associated with Paraesophageal Hernia: Angiocardiographic Study of a Case*

ISRAEL STEINBERG, M.D., F.C.C.P.
New York, New York

Aspiration pneumonia due to ingestion of mineral oil for a laxative has become recognized in the apparently healthy;[1-4] its occurrence in weak, debilitated and chronically ill infants, children and adults is probably better known.[5-7] Dysphagia and cardiospasm, because they are associated with regurgitation, have also become well established as causes of lipoid pneumonia.[8-12]

The purpose of this report is to re-emphasize the importance of a high index of suspicion that patients with chronic pulmonary infiltration may have lipoid pneumonia. Despite the suggestive appearance

*From the Departments of Medicine and Radiology, The New York Hospital-Cornell Medical Center.
Aided by a grant from the Mallinckrodt Chemical Works.

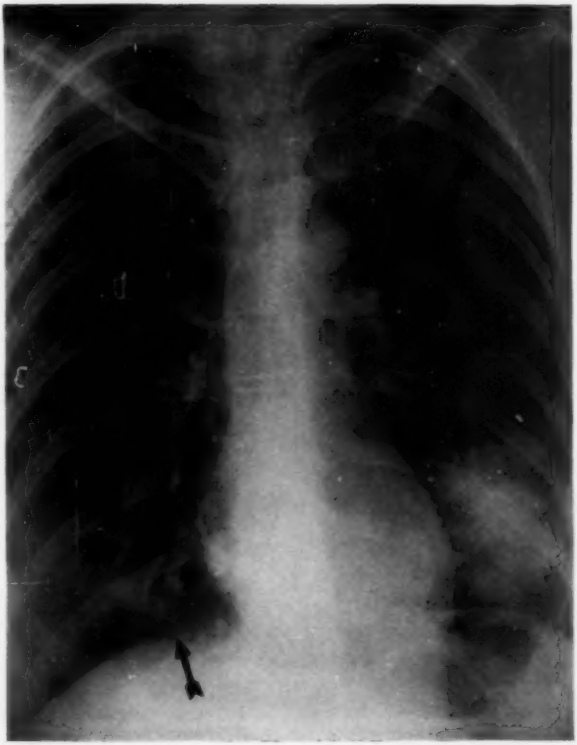


FIGURE 1. Frontal teleroentgenogram shows a large rounded spun-glass density at the left base. Diffuse, fine granular densities are also present at the right base (arrow).

of the roentgenograms in the case herein reported, 13 years elapsed before a history of ingestion of mineral oil for laxative purposes was elicited. An unsuspected paraesophageal hernia may have contributed to the aspiration penumonia. Finally, the angiocardiographic findings of the pulmonary circulation in lipoid pneumonia, probably reported for the first time, are presented.

Report of a Case

A 33 year old former schoolteacher (N.Y.H. No. 765989) was referred on April 28, 1957, by Dr. Raymond E. Miller because the chest roentgenogram suggested aspiration pneumonia. Thirteen years prior to admission she was asked to set her pupils an example by having a chest roentgenogram in a mobile chest roentgenographic unit. Her film was the only abnormal one; subsequently she was told that it contained a rounded ball-like shadow in the left side with a smaller one in the right lung. Visits to several physicians and bronchoscopy failed to establish a diagnosis. Because of the insistance of the schoolboard for repeated examinations, and because she was suspected of having tuberculosis, although she was asymptomatic, the patient gave up teaching and became a secretary. The roentgenogram (Fig. 1) shows a large rounded "spun-glass" density at the left base and a smaller fine linear coalescent density at the right base that immediately suggested the possibility of mineral oil pneumonitis. Direct questioning then elicited a history of ingestion of one to four teaspoonful doses of mineral oil before retiring every evening. She denied dyspnea, cough or expectoration.

Physical examination revealed a well developed and nourished woman in no distress. The gag reflex was diminished. The only abnormal physical findings were dullness and decreased breath sounds at the left base. The heart was not enlarged and there were no murmurs; the blood pressure was 128/80 mm. Hg. Studies of the blood and urine were normal. The sputum did not contain lipids.

Gastrointestinal studies revealed an unsuspected large (8 cm. in diameter) paraesophageal hernia (Fig. 2). Angiocardiography disclosed absent pulmonary arterial circulation in the anterior and lateral basal segments of the left lower lobe, the site of the infiltration (Fig. 3A). Similarly, the pulmonary venous circulation of the anterior and lateral basal segments of the left lower lobe were also absent (Fig. 3B). Bronchoscopy revealed no abnormalities of the tracheobronchial system. The aspiration specimen of the lower lobes contained many lymphocytes and macrophages, but

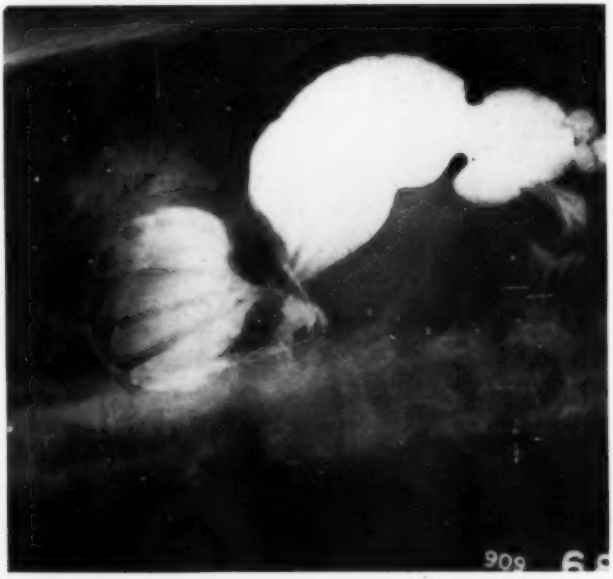


FIGURE 2. Roentgenogram showing a large paraesophageal hernia.

lipids were not present in the latter. Smear and cultural studies were negative. Bronchography showed the tracheobronchial system to be normal except for poorly filled anterior and lateral basal segments of the left lower lobe (the region of the pneumonitis) — (Fig. 4). Mineral oil ingestion was stopped and re-examination, a year later, showed the patient to be asymptomatic; the chest roentgenogram was unchanged.

Discussion

Lipoil (mineral oil) pneumonia is difficult to diagnose in the absence of a history of ingestion or medication of the throat and nasal passages with mineral oil. Chronic pulmonary diseases (bronchiectasis, tuberculosis, fungus, sarcoidosis and neoplasm) may simulate lipoid pneumonia. Indeed, the recent literature records accounts of lipoid pneumonia becoming recognized only after extensive resectional surgery. In several instances, had the diagnosis been established, surgery would have been obviated and segmental or lobar excisions made with preservation of pulmonary function.[2,13-16]

In the absence of history of aspiration of lipoid material, the diagnosis can be established by cytologic and histochemical study of the sputum or material obtained by aspiration biopsy of the lung.[1,7,12,17,18] In the case reported above, special (Papanicolaou) studies of the bronchial tree obtained by injection and aspiration of saline at bronchoscopy failed to show macrophages containing lipoid granules.

Although a definite diagnosis of lipoid pneumonia cannot be made from the roentgenographic studies alone, the diffuse bilateral, lower lung field "spun or ground-glass" appearance (Fig. 1) is highly suggestive of mineral oil pneumonitis.[7,19] The bronchogram (Fig. 4) with obstruction of the terminal bronchi of the involved areas is also a common finding in lipoid pneumonia.[7,19] These, coupled with the history of habitual use of mineral oil as a laxative establish the diagnosis of lipoid pneumonia.

Mineral oil is a non-irritating, insoluble hydrocarbon which readily flows from the pharynx into the tracheobronchial tree without causing cough or reflex closure of the glottis. Furthermore, mineral oil hinders ciliary movement and mucous secretion enhancing alveolar aspiration of the foreign material. Experimentally, mineral oil causes pulmonary capillary edema and albumin seepage into alveoli. A reticulum of collagenous fibers surround macrophages containing mineral oil droplets and the mineral oil becomes fixed in fibrous tissues obliterating many air spaces and eventually causes an oil granuloma.[7,20]

The finding of a paraesophageal hernia in the patient reported above (Fig. 2) raises the questions of its role in aspiration of mineral oil. Since the patient took the laxative prior to retiring and because oil rises to the top of emulsions, it may be that its presence in the thorax in concentrated form favored passage into the tracheobronchial system and lung.

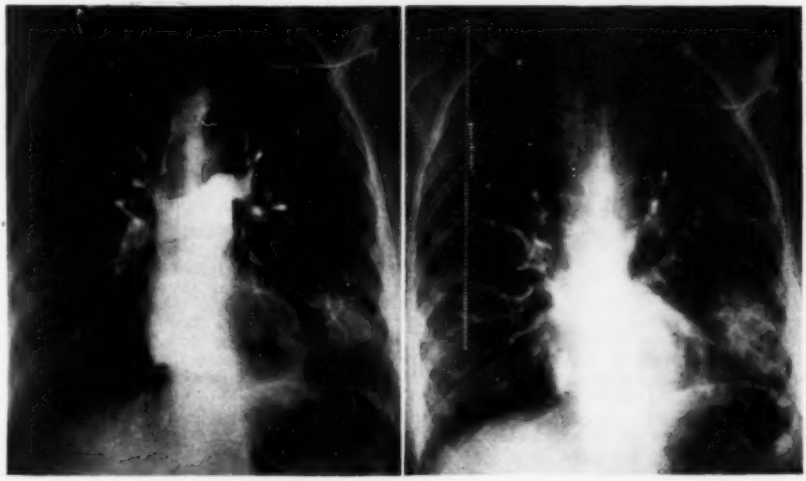


FIGURE 3A FIGURE 3B

FIGURE 3. Frontal teleangiocardiograms. *A*. There is absence of the pulmonary arterial circulation in the region of the left lower lobe density. *B*. The pulmonary venous circulation of some of the segments of the left lower lobe is also absent. In both studies, the large paraesophageal hernia containing air is readily visualized.

Angiocardiography (Fig. 4) revealed that the pulmonary circulation was cut off in the region of the lipoid pneumonia. This finding is in keeping with the damage to the pulmonary circulation observed in experimental lipoid pneumonia.[20] Caution must, therefore, be used in attributing decreased vascularity of the lungs to bronchogenic cancer;[21,22] particularly because many pulmonary diseases (especially tuberculosis) show this phenomenon.[23]

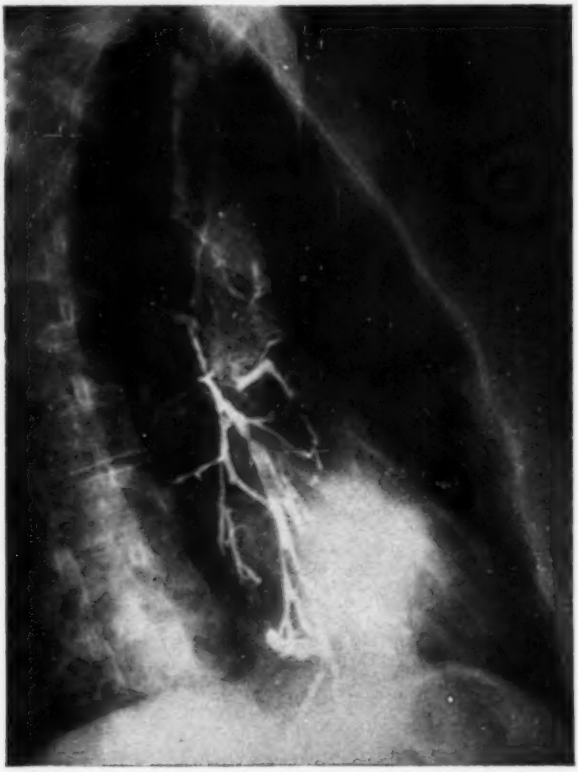


FIGURE 4. Bronchogram showing poorly filled anterior and lateral basal segments of the left lower lobe, the site of lipoid pneumonia.

SUMMARY

An asymptomatic adult with bilateral lower lung field infiltrations went 13 years before the history of nightly ingestion of mineral oil was elicited. An unsuspected paraesophageal hernia was also found and may have contributed to mineral oil aspiration and lipoid pneumonia. Bronchography showed obstruction of the bronchi leading to the involved segments. Angiocardiography revealed avascularity of the lung in the regions of the lipoid areas, probably because the pulmonary circulation was destroyed by fibrotic changes early in the disease. A year after cessation of mineral oil ingestion the patient was asymptomatic; no change in the chest roentgenogram could be detected. Surgical repair of the paraesophageal hernia did not seem warranted because of the asymptomatic state.

RESUMEN

Un adulto asintomático, con infiltraciones bilaterales de las dos bases lumonares pasó 13 años antes de que se descubriera por su historia, que ingería todas las noches aceite mineral.

Se encontró que tenía también una hernia para-esofagina no sospechada que pudo haber contribuído a facilitar la aspiración del aceite mineral y la creación de la neumonía lipóidica.

La broncografía demostró la obstrucción de los bronquios que iban hacia los segmentos compormetidos. La angiocardiografía reveló la falta de vascularización del

pulmón en las áreas de la afección lipóidica probablemente porque la circulación pulmonar se destruyó por cambios fibrosos desde el principio de la enfermedad. Un año después de haber cesado la ingestión de aceite mineral, el enfermo era asintomático y ninguna modificación en el aspecto radiológico pudo notarse. El tratamiento quirúgico de su hernia esofagina no se consideró pertinente por ser asintomática.

RESUMÉ

Un adulte ne présentant pas de symptômes particuliers était atteint d'infiltrations bilatérales de la partie inférieure du champ pulmonaire. Il fallut 13 ans avant qu'on put mettre à jour l'histoire d'une ingestion nocturne d'huile minérale. On trouva également une hernie para-oesophagienne insoupçonnée et qui a pu contribuer à l'aspiration d'huile minérale et à la pneumonie lipoïdique. La bronchographie montra l'obstruction des bronches conduisant aux segments atteints. L'angiocardiographie révéle une absence de vascularisation du poumon dans les régions de l'atteinte lipoïdique, probablement parce que la circulation pulmonaire avait été détruite par des altérations fibreuses précoces pendant la maladie. Un an après la cessation d'ingestion d'huile minérale, le malade n'avait plus aucun symptôme et on ne put mettre en évidence aucune altération des clichés thoraciques. Une réparation chirurgicale de la hernie para-oesophagienne ne sembla pas souhaitable étant donné l'absence de toute manifestation pathologique.

ZUSAMMENFASSUNG

Entdeckung eines symptomenfreien Erwachsenen mit bilateralen Infiltrationen der unteren Lungenabschnitte, der angab, vor 13 Jahren nachts Petroleum verschluckt zu haben. Ausserdem fand sich unerwarteter Weise eine paraesophageale Hernie, die zu der Petroleumaspiration und Lipoidpnumonie beitragen haben könnte. Die Bronchographie zeigte einen Verschluss der zu dem betreffenden Segmenten führenden Bronchien. Die Angiocardiographie ergab eine Gefässlosigkeit der Lunge in den Gebieten der Lipoidablagerungen, möglicherweise infolge Zerstörung der pulmonalen Zirkulation durch fibrotische Vorgänge in früheren Krankheitsstadien. Ein Jahr nach Beendigung der Einahme von Petroleum war der Patient Symptomenfrei; eine Veränderung in den Thoraxröntgenbildern konnte nicht festgestellt werden. Wegen des erscheinungsfreien Zustandes schien eine chirurgische Beseitigung der paraesophagealen Hernie nicht gerechtfertigt.

REFERENCES

1 Schneider, L.: "Pulmonary Hazard of the Ingestion of Mineral Oil in the Apparently Healthy Adult: A clinicoroentgenologic study with a report of five cases," *New England J. Med.* 240:284, 1949.

2 Baron, E.: "Lipoid Pneumonia Due to Use of Mineral Oil as Laxative," *Virginia M. Month.* 77:448, 1950.

3 Mason, J. M. III.: "Lipoid Pneumonia — Adult Type: Report of a Case and Discussion of the Subject," *Ann. Surg.* 141:940, 1955.

4 Meyers, J. B., and Griffith, R. L.: "Lipoid Pneumonia Due to Prolonged Ingestion of Mineral Oil," *Dis. Chest* 27:677, 1955.

5 Bromer, R. S., and Wolman, I. J.: "Lipoid Pneumonia in Infants and Children," *Radiology* 32:1, 1939.

6 Freiman, D. G.; Engelberg, H., and Merritt, W. H.: "Oil Aspiration (Lipoid) Pneumonia in Adults: Clinicopathologic Study of the Forty-seven Cases," *Arch. Int. Med.* 66:11, 1940.

7 Volk, B. W.; Nathanson, L.; Losner, S.; Slade, W. R., and Jacobi, M.: "Incidence of Lipoid Pneumonia in a Survey of 389 Chronically Ill Patients," *Am. J. Med.* 10: 316, 1951.

8 Belcher, J. R.: "The Pulmonary Complications of Dysphagia," *Thorax* 4:44, 1949.

9 Breakey, A. S.; Dotter, C. T., and Steinberg, I.: "Pulmonary Complications of Cardiospasm," *New England J. Med.* 245:441, 1951.

10 Lake, R. A.: "Pulmonary Changes Related to Cardiospasm," *Ann. Int. Med.* 35:593, 1951.

11 Andersen, H. A.; Holman, C. B., and Olsen, A. M.: "Pulmonary Complications of Cardiospasm," *J.A.M.A.* 151:608, 1953.

12 Steinberg, I., and Finby, N.: "Lipoid (Mineral Oil) Pneumonia and Cor Pulmonale Due to Cardiospasm: Report of a Case," *Am. J. Roentgen. & Rad. Therapy* 76:108, 1956.

13 Jampolis, R. W.; McDonald, J. R., and Clagett, O. T.: "Mineral Oil Granuloma of Lungs: Evaluation of Methods for Identification of Mineral Oil in Tissue," *International Abstracts of Surg.* 97:105, 1953.

14 McDonald, J. R., and Hodgson, C. H.: "Problem of Lipoid Pneumonia or Granuloma of Lung," *Med. Clin. North America* 38:989, 1954.

15 Davis, E. W.; Hampton, A. O.; Bickman, C. E., and Winship, T.: "Lipoid Pneumonia Simulating Tumor," *J. Thoracic Surg.* 28:212, 1954.

16 Stonehill, S., and Bodon, G. R.: "Massive Lipoid Granuloma of Lung and its Treatment," *Ann. Int. Med.* 42:432, 1955.

17 Nathanson, L.; Frankel, D., and Jacobi, M.: "Diagnosis of Lipoid Pneumonia by Aspiration Biopsy," *Arch. Int. Med.* 72:627, 1943.

18 Farber, J. F.; Carpenter, T., and Pellicano, V.: "Lipoid Pneumonia: Diagnosis by Aspiration Biopsy," *Am. Rev. Tuberc.* 45:453, 1942.

19 Hampton, A. O.; Bickman, C. E. Jr., and Winship, T.: "Lipoid Pneumonia," *Am. J. Roentgenol. and Rad. Therapy* 73:938, 1955.

20 Cannon, P. R., and Walsh, T. E.: "Lipoid Pneumonia and Some Potential Dangers of Intranasal Medication," *New Internat. Clin.* 3:109, 1938.

21 Keil, P. G.; Voelker, C. A., and Schissel, D. J.: "Diagnostic Value of Pulmonary Arteriography in Bronchial Carcinoma," *Am. J. Med. Sci.* 219:301, 1950.

22 Keil, P. G., and Schissel, D. J.: "The Differential Diagnosis of Unresolved Pneumonia and Bronchogenic Carcinoma by Pulmonary Angiography," *J. Thoracic Surg.* 20:62, 1950.

23 Dotter, C. T., and Steinberg, I.: *Angiocardiography*, Paul B. Hoeber, Inc., New York, 1951.

Excavated Haematomas after Pulmonary Segmental Resection*

H. M. BEUMER, M.D. and T. L. MELLEMA, M. D.
Bilthoven, Netherlands

Since 1949 pulmonary segmental resection has been increasingly employed in the treatment of pulmonary tuberculosis in the Sanatorium Berg en Bosch.[1]

From December 1956 on there appeared in the postoperative course of patients with segmental resection in a number of cases a remarkable and interesting phenomenon.

The surgeon attaches, after the extirpation of one or more segments, the borders of the intersegmental plane to each other. In this way a situation is created, whereby the denuded lung-surfaces, on the place of the extirpated segments, lie on each other.

There is little or no doubt that there are leaking alveoli and capillaries in this intersegmental plane. The presence of a haematoma in the intersegmental plane is therefore a frequently appearing phenomenon without complications.

The development of an excavated haematoma, as seen several times since December 1956, was rather unusual. The excavated haematomas never caused complications, but it seemed to us interesting to communicate these observations, because they have till now not been described in the literature and especially because the excavated haematoma could be confused with a cavity.

It seemed possible that a correlation exists between the frequent development of the excavated haematomas and the new suction drainage, in use since December 1956. That month the first bilateral segmental resection through simultaneous anterior thoracotomy and transverse sternotomy was performed. After this operation it was desirable to expand the lungs as soon and as completely as possible.[2] Therefore a new suction system came into use with a constant negative suction varying between 40 and 100 cm. of water.

It was found that the lung expansion generally was excellent, but also that the postoperative intrathoracic serosanguineous effusion could be removed completely. The results were significantly better than after the unilateral segmental resection. Patients, operated before December 1956, have been connected to a closed drainage system maintaining a negative suction of only 8-10 cm. of water.

Because of the good results with the strong suction drainage after the bilateral simultaneous segmental resections, this method came into use after the unilateral segmental resections too.

To find out if strong suction drainage was responsible for the development of excavated haematomas, we reviewed all cases where segmental resection had been performed.

Between December 1956 and September 1958, 342 segmental resections were performed. In this group 16 excavated haematomas developed

*From the Sanatorium Berg en Bosch.

(=4.7 per cent). With this compare: in the preceding period a group of 248 segmental resections has been considered. Excavated haematomas occurred only twice (=0.9 per cent).

It must be noted that the technique of resection did not change since 1950 (surgeon: M. C. A. Klinkenbergh, M.D.).

We conclude therefore that excavated haematomas become significantly more frequent with stronger suction drainage. The development of the excavated haematoma is possibly as follows. After the segmental resection a narrow fissure exists within the lobe with on both sides a denuded lung surface, with leaking alveoli and capillaries. A certain amount of blood will collect in this intersegmental plane, and cause a small solid haematoma, also in cases where no strong negative suction through the drainage catheters is used. This small solid haematoma in the intersegmental plane is therefore a common observation. This can readily be caused by the positive pressure of the blood in the vessels. Air, however, present in the alveoli, where normally a negative pressure is maintained, can only enter into the intersegmental plane by a suction force. Therefore we hold the opinion that previously no air occurred in the haematomas, but since December 1956 could frequently be observed.

On the roentgenogram the pictures of the excavated haematoma all look alike: a thick wall, probably consisting of clotted blood, and a central cavity. The roentgenological picture is highly typical for a cavity with a thick wall. This picture cannot be caused by pulmonary atelectasis, which have another aspect. Why the wall of the cavity consists of clotted blood and why the air is in the central cavity cannot be explained. As a matter of fact one should expect in some cases a cavity with a certain amount of fluid. Sometimes a small quantity of fluid can be shown in the excavated haematoma, but this fluid always disappears within a few days. As a rule the excavated haematoma is first seen on the x-ray film of the second day after the operation, at the moment that the suction drainage is terminated. This proves that the excavated haematomas develop in the immediate postoperative period during the suction drainage.

In several cases the standard x-ray film of the chest does not strictly prove the excavated haematoma, because of the fact that the patient lies in his bed and has serious pain complaints in the chest, so most of the air is expired from the lungs.

The proof in these cases is given by the tomograms as soon as these can be performed. As a rule this is possible the fourth or fifth postoperative day.

The average time in which excavation occurred was four weeks, with variations from 12 days until three months. The air in the excavated haematoma is resorbed quickly. Generally this period varies from a few days to a few weeks.

The bloodclots however remain present during a longer period. Sometimes it takes several months before this coagulum has disappeared.

At last there remains, even when the excavated haematoma has been large, only a little fibrous tissue.

The highest temperature ever measured was 39.2°C. Sometimes a short period of subfebrile temperatures developed, but in general the

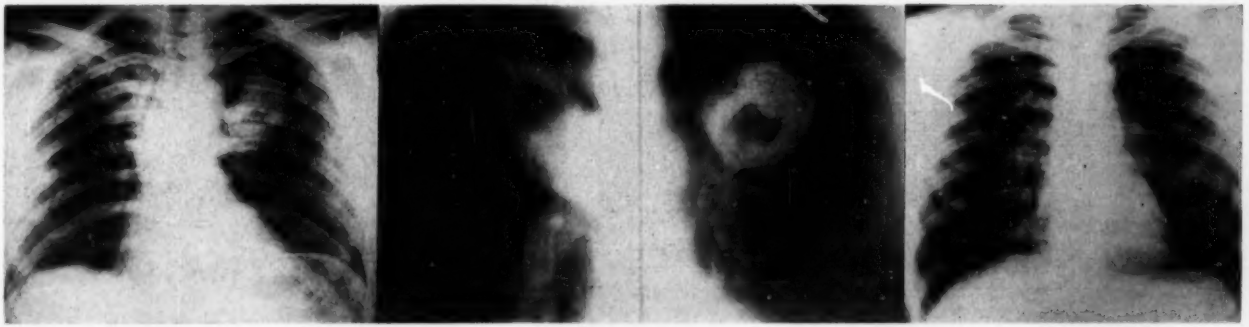


FIGURE 1(a) FIGURE 1(b) FIGURE 1(c)

FIGURE 1 (a): X-ray film of a man of 27 years on the second day after operation, showing where simultaneous bilateral segmental resection was performed (left: apicodorsal segment upper lobe; right: apical segment upper lobe). FIGURE 1 (b): The seventh day the planograms clearly showed cavity on both sides. FIGURE 1 (c): At the moment of departure from the Sanatorium only minimal rests could be shown. This is the only case of biolateral excavated haematomas on more than 60 bilateral simultaneous segmental resections.

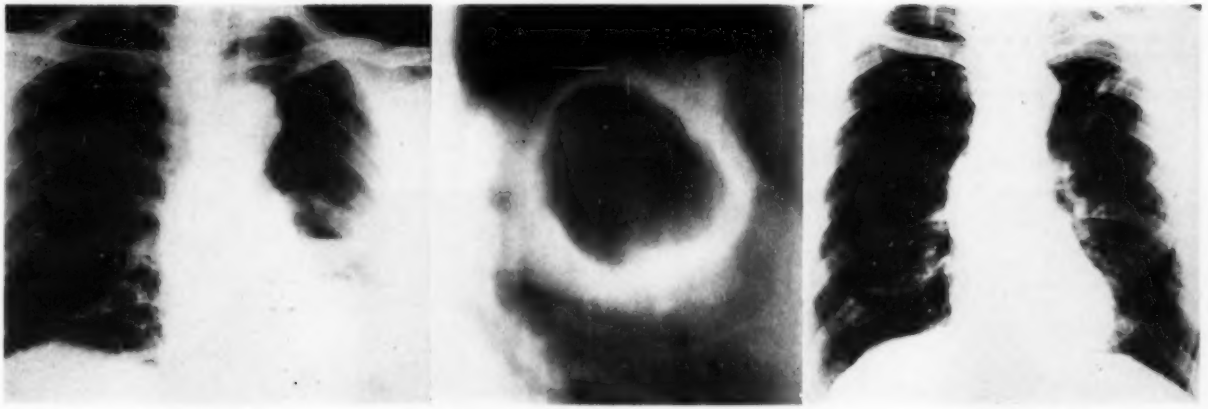


FIGURE 2(a) FIGURE 2(b) FIGURE 2(c)

FIGURE 2(a): Showing a 38 year old man. The apicodorsal segment of the left upper lobe was removed two days before. A clear cavity is visible. FIGURE 2(b): Five days after the operation a giant cavity has developed. FIGURE 2(c): After five months only a minimal rest is visible.

excavated haematoma passed uneventfully. Never were there signs of a bronchial fistula. Therefore we must consider the leaking alveoli as the only source of air for the excavated haematoma.

Some typical cases of excavated haematomas are illustrated.

SUMMARY

Between December, 1956 and September, 1958, 342 segmental resections were performed in the Sanatorium Berg en Bosch. In this group, 16 excavated haematomas developed in the intersegmental plane. Generally, the excavated haematoma disappeared spontaneously, without any symptom of complications.

The cause is considered to be the strong negative suction in the drainage catheters, between 40 and 100 cm. of water, in use during the postoperative period.

RESUMEN

Entre Diciembre de 1956 y Septiembre de 1958, se hicieron 342 resecciones segmentarias en el Sanatorio Berg en Bosch. En ste grupo se presentaron 16 hematomas excavados en el plano intersegmentario.

Generalmente el hematoma excavado desapareció espontáneamente sin síntomas y sin complicaciones.

Se considera que la causa es la succión fuertemente negativa en los catéteres, entre 40 y 100 cms. de agua que se usa durante el postoperatorio.

RESUMÉ

Entre décembre 1956 et septembre 1958, 342 résections segmentaires furent pratiquées au Sanatorium Berg en Borsch.

Dans ce groupe, 16 hématomes excavés se développèrent dans le plan intersegmentaire. Généralement, l'hématome excavé disparut spontanément. sans complications.

Les auteurs pensent que la cause en est la forte aspiration négative du drainage par sonde, entre 40 et 100 cm. d'eau, utilisé pendant la période post-opératoire.

ZUSAMMENFASSUNG

In der Zeit zwischen Dezember 1956 und September 1958 wurden im*Sanatorium Berg en Bosch 342 Segmentresektionen vorgenommen. In dieser Gruppe haben sich 16 exkavierte Haematome in der Intersegmenttalebene gebildet. Es bildete sich das exkavierte Haematom* spontan zurück ohne irgendwelche Symptome oder Komplikationen.

Man nimmt als Ursache den hoch negativen Sog (zwischen 40 und 100 cm Wasser) an in dem Drainage-katheter, wie er während der postoperativen Periode gebraucht wird.

*im allgemeinen

REFERENCES

1 Hirdes, J. J., and Stegerhoek, C. I.: "Resection in Pulmonary Tuberculosis, Results and Follow up of 700 Cases," *Dis. Chest* 30:277, 1956.

2 Van Zuiden, N.: *Nederl. Tijdschr. Geneesk.* 102:2124, 1958.

Experience with Seromycin* in Tuberculosis**

CHARLES K. PETTER, M.D., F.C.C.P.,[1] and VICTOR Y. K. TYAU, M.D., F.C.C.P.[2]
Waukegan, Illinois

Following the discovery of the antibiotic Seromycin by Harned and Kropp in 1955, a good deal of enthusiasm became manifest for this new weapon against tuberculosis.

We became interested in 1956 when the substance was made available for clinical study and have used it since that time. This use is not general as yet, but rather as an adjutant to the other accepted forms of drug therapy where results are not as desired.

In July 1956, we began the use of Seromycin and up to August 1958 prescribed it in 35 cases of tuberculosis which are narratively described herewith. The dose was 250 milligrams twice daily.

This group of 35 persons had moderate to far advanced pulmonary tuberculosis which had not responded to dihydrostreptomycin, paraminosalicylic acid and isonazid regime which had been in effect for three months or more.

Each of these persons had acid-fast organisms in the sputum at onset of therapy and three had extrapulmonary lesions as well.

Skin tuberculosis	1
Vertebral (bone) tuberculosis	1
Cervical lymph node tuberculosis	1

Five of the patients had concomitant diabetes; none of these was severe, but all were controlled with modified diet and 15 to 30 units of insulin daily.

The group consisted of 23 men and 12 women; 31 whites and 4 Negroes. The age range was from 25 to 82.

At the onset of treatment a complete blood study was made along with a urinalysis, P.S.P. determination, blood urea nitrogen and bromsulphalein determination. These studies were repeated every four to six weeks during the administration of the drug and in all cases these tests remained within the range of normal. At each four to six week interval sputum examinations and chest x-ray film studies were made. When the sputum studies (smears) became negative a study, by culture, of the fasting gastric contents was instituted.

This sries of patients was, incidentally, a supervised sanatorium group, some of whom were followed in the out-patient clinic when sputum became negative.

In this report we refrain from a presentation of chartsand tables, but prefer to adhere to a narrative summary and conclusion. A summary of observations and results shows, first of all, no unfavorable change in the blood cytology, erythrocyte sedimentation rate or hemoglobin con-

*Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.
**Presented at the Fifth International Congress on Disease of the Chest, American College of Chest Physicians, Tokyo, Japan, September 7-11, 1958.
[1]Superintendent and Medical Director, Lake County Tuberculosis Sanatorium; Associate in Medicine, Stritch School of Medicine, Loyola University.
[2]Assistant Medical Director, Lake County Tuberculosis Sanatorium.

tents. Secondly, there has been no evidence of impaired kidney function with the administration of Seromycin. Thirdly, there was no evidence of liver damage. (BSP)

Three patients did show some psychopathic changes. These were manifest by (1) a change of personality and (2) a state of elation. One required electric shock therapy to bring her back to normal personality. Two others recovered from their "highness" by withdrawal of the drug for a week of ten days. All three of these were put back on Seromycin in smaller doses which were slowly stepped up, without further difficulty. Of the 35 persons treated for six months or more, (maximum, one year):

28 showed overall improvement.
5 showed no change in general condition.
2 became worse and subsequently died (1 negress; 1 white man).
26 (72 per cent) had conversion of sputum to negative.
24 (67 per cent) had x-ray evidence of improvement.
9 had no x-ray evidence of improvement.
2 had x-ray evidence of worsening.

Of this group then, 26 (72 per cent) were benefited by the administration of Seromycin where other drug therapy regimens had failed.

All in all we are glad to have Seromycin and believe that its judicious use under careful observation is a distinct addition to our armamentarium in combating tuberculosis. No patients in the series, even those who did not respond clinically, showed drug resistant organisms.

The Evaluation of Roentgen Therapy in the Management of Non-Resectable Carcinoma of the Lung

HARRY L. BARTON, M.D., G. M. McGRANAHAN, JR., M.D., and GEORGE L. JORDAN, JR., M.D.

Houston, Texas

Carcinoma of the lung may be treated successfully by surgical excision when the lesion is confined to the lung; however, in the majority of patients the disease is too far advanced for any type of excisional therapy when the diagnosis is established. Therefore, most patients must be offered some other modality of therapy or left untreated. Roentgen therapy is often employed but its value is disputed. There are those who maintain that no patient benefits, while others maintain that most patients may be improved. When the average duration of life is studied the picture is dismal, regardless of therapy, for life expectancy usually does not exceed six months. Ariel and his co-workers found that the average duration of life in patients treated with deep x-ray therapy, in histologically proved lesions, was 5.0 months as compared to a survival of 4.2 months in patients receiving no treatment.[1] Watson gives a similar report in a review of 611 cases in which the duration of life without therapy was 3.1 months as compared to 5.7 months with radiotherapy.[6] In view of the fact that therapy often requires one month for administration, the differences in survival rates reported are insignificant.

On the other hand, there are reports of patients who have survived for long periods following roentgen therapy. Shultz found that no patient survived as long as two years without treatment, whereas 5 per cent of treated patients in his series survived for this period, and four (1 per cent) of those treated survived five years.[4] Smithers reports a five year survival rate of 4.1 per cent in patients with non-resectable lesions who are treated by x-ray.[5]

Regardless of the effect upon longevity, roentgen therapy must be considered as an aid in palliation. Blanshard reported success in 83 per cent of 35 patients treated for relief of symptoms.[2]

This study was undertaken to assess the effect of roentgen therapy with regard to relief of symptoms and the prolongation of life at the Veterans Administration Hospital, Houston, Texas.

Material

The records of all patients having a diagnosis of carcinoma of the lung admitted to the Veterans Administration Hospital, Houston, Texas, from April, 1949 through December, 1956 were reviewed. Those who were treated by surgical excision of their tumor, those in whom the diagnosis was made only at necropsy, and those who had received treatment elsewhere, were excluded from the study. Also excluded were patients in

From the Department of Radiology and Surgery, Veterans Administration Hospital, and Baylor University College of Medicine.

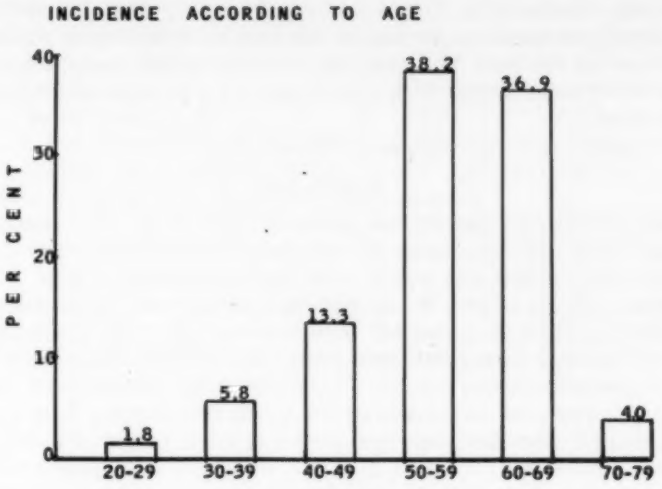


TABLE 1

whom the diagnosis was made only on clinical evidence. There remained 225 patients with histologic evidence of carcinoma of the lung who received primary treatment in this hospital. Thirty-nine were found to have a non-resectable tumor at the time of exploratory thoracotomy, while 186 were considered inoperable on the basis of bronchoscopic findings or on the basis of distant metastases.

All were men. The age range was 25 to 79 years, and the diagnosis was most commonly made in those in the 6th and 7th decades (Table 1). Almost two-thirds of the tumors were squamous cell type (Table 2).

The usual admitting complaints were cough, pain, loss of weight, shortness of breath, hemoptysis, or a combination of these symptoms, but, as in other studies, the symptoms depended upon the location of

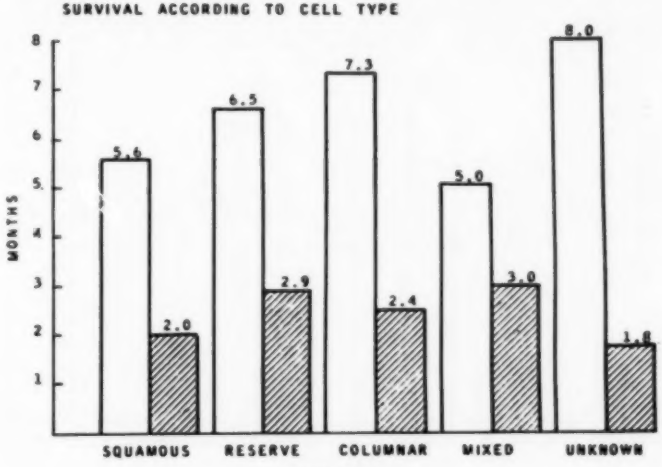


TABLE 2

the tumor. Included in this series were 21 whose first symptoms were neurologic, presumed to be due to cerebral or spinal cord metastases. Of interest is the fact that there were seven totally asymptomatic patients, the lesion having been discovered on a routine roentgenogram of the chest.

One hundred per cent follow-up was achieved.

Treatment

One hundred and twenty-two patients were given only symptomatic and supportive therapy, while 103 received radio-therapy. Since all had far-advanced disease, the tumor dose was calculated to give optimum palliation without adding to the patient's discomfort. When the disease appeared localized, a potential curative dose of 5,000 roentgens was delivered through four ports over a four and one half week period. The dose was administered with 220 KV machine with a half value layer of 2 mm. of copper, 50 cms. distance, with the size of ports to conform to the primary tumor and enlarged nodes in each patient. In many instances a considerably lower tumor dose was given to minimize systemic, cutaneous, or pulmonary reactions, and to avoid production of general debility.

Results

All of the 225 patients were dead at the time the study was undertaken. The longest survival of a patient without roentgen therapy was 22 months, while in the treated patients the longest survival was 42 months. The average survival time for those patients without therapy was 1.9 months as compared to an average of 5.9 months with roentgen therapy. When those patients who died within one month without treatment, and, therefore, would not have been considered candidates for radio-therapy, are excluded from the tabulation, the average survival rate for the untreated patients is 2.3 months.

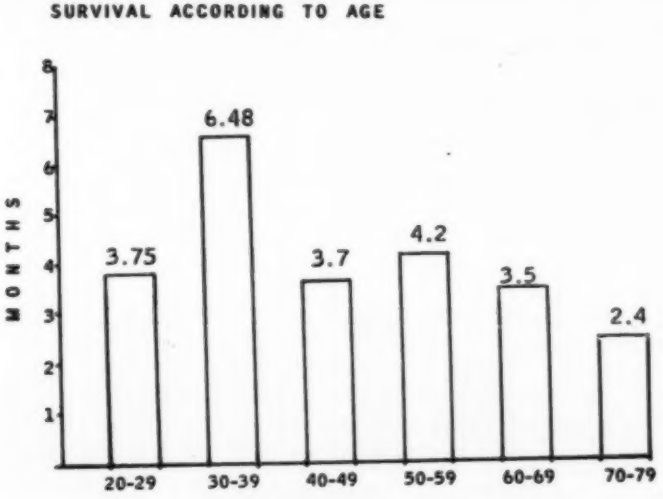


TABLE 3

Records concerning relief of symptoms are admittedly unprecise and subjective. Nevertheless, sufficient data were recorded in the charts to show complete relief of symptoms in approximately 20 per cent, while an additional 50 per cent received partial or moderate relief of symptoms. The remaining 30 per cent had no benefit. These records were made by the physician caring directly for the patient rather than by the radio-therapist. Progress notes by the therapist are much more optimistic and suggest a more favorable response.

Analysis of these data indicates that age had no appreciable effect upon survival time. Those in the fourth decade had the longest average survival time, but the total number is not large enough to draw the conclusion that those in this age group live longer. However, the concept that the younger patients have more rapid tumor growth is not valid when one is dealing with non-resectable lesions (Table 3).

An analysis according to cell type showed that this factor made little difference in the survival rate. Whereas, superficial inspection of these figures would indicate that the columnar cell carcinoma is more responsive to roentgen therapy than other types, the number of cases is so small that there is no statistically significant difference between the survival time in the treated and untreated. In patients with squamous cell carcinoma the difference between the two groups is statistically significant ($p<.001$), (Table 4).

INCIDENCE ACCORDING TO CELL TYPE

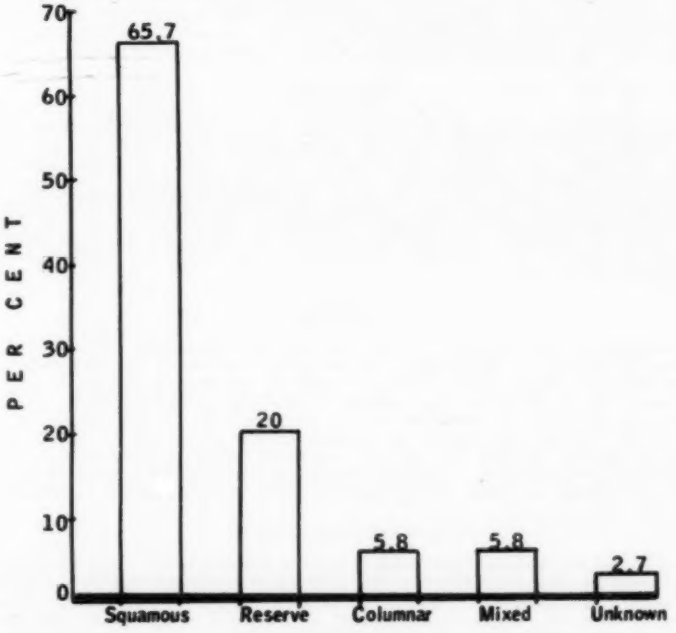


TABLE 4

Discussion

Our data indicate that roentgen therapy may prolong life, but that the average increase in survival time is only three months. In other studies, as previously noted, the increase in survival time is even less striking. Consequently, it becomes almost a matter of philosophy as to whether one should treat an asymptomatic patient, particularly if hospitalization is required for roentgen therapy, when the anticipated increase in survival is so short.

On the other hand, there seems little doubt concerning the value of x-ray therapy in those patients with symptoms. Although not all will be relieved, the incidence of improvement is so high that its value is unquestionable. Therefore, radio-therapy is to be recommended whenever symptoms exist.

Other studies have indicated that certain types of tumors are more responsive to x-ray treatment than others, thus Kutz found that squamous cell carcinoma responded well, while treatment of undifferentiated types was ineffective.[3] Our study does not support this contention, and it is our feeling that all types of carcinomas should be treated regardless of the cell type. It is of interest that the patients with squamous cell carcinomas had the shortest survival time. It is this cell type which is responsible for the majority of longterm survival in surgically treated patients. It would thus appear that squamous cell is more likely to remain localized during a period when active surgical intervention is possible than other histologic types, but once the tumor has broken its bounds and disseminated to the point of becoming non-resectable, cell type is of little importance. Under such circumstances all types of carcinoma of the lung are highly malignant, and the survival time is short.

It was discouraging to find that the mortality rate had been 100 per cent. One would have hoped for at least one five-year survival out of 225 cases. Failure of any patient to live for this period again points out the poor prognosis in this disease and it is to be hoped that new modalities will be forthcoming in the near future. Nevertheless, until such time, x-ray will maintain its place as a valuable therapeutic agent when administered judiciously.

SUMMARY

The records of 225 patients with non-resectable carcinomas of the lung were reviewed. One hundred and three were given treatment with roentgen therapy, while 122 had only supportive therapy. All were dead at the time of the study, the longest survival time being 42 months. Patients treated with x-ray lived an average of 5.2 months as compared with a survival of 1.9 months in the untreated cases. In treated patients symptoms were partially or completely relieved in 70 per cent. It is concluded that x-ray therapy is a valuable agent in the control of symptoms in inoperable carcinoma of the lung and may, at times, result in prolongation of life.

RESUMEN

Se han revisado las historias de 225 enfermos de carcinoma pulmonar no resecable. A 103 se les aplicó Roentgenterapia en tanto que en 122 sólo se usó la terapia de sóporte. Al hacer este estudio todos habían muerto, siendo la mayor sobrevida de 42 meses. Los pacientes tratados con roentgenterapia sobrevivieron 5.2 meses por término medio, en tanto los casos no tratados sólo sobrevivieron 1.9 meses. En los casos tratados los síntomas fueron aliviados completa o parcialmente en el 70 por ciento de los casos. Se concluye que la roentgenterapia es útil agente para el control de los síntomas del carcinoma inoperable del pulmón y a veces puede obtenerse con él la prolongación de la vida.

RESUMÉ

Les dossiers de 225 malades atteints de cancers inopérables du poumon ont été étudiés. 103 subirent un traitemen radiothérapique, tandis que 122 ne reçurent qu'une thérapeutique palliative. Tous étaient décédés au moment de l'étude, la plus longue survie ayant été de 42 mois. Les malades traités par la radiothérapie vécurent une moyenne de 5,2 mois comparativement à une survie de 1,9 mois pour les cas non traités. Chez les malades traités, les troubles furent partiellement ou complètement soulagés dans 70% des cas. Les auteurs concluent que la radiothérapie est un agent de valeur pour supprimer les manifestations cliniques du cancer inopérable du poumon. Elle peut, de temps en temps, être à l'origine d'une prolongation de l'existence.

ZUSAMMENFASSUNG

Durchsicht der Krankengeschichten von 225 Patienten mit nicht mehr operablen Lungencarzinom. 103 erhielten eine Behandlung mit Röntgenstrahlen, während 122 nur allgemein unterstützend behandelt wurden. Z.Zt. der Untersuchung waren alle verstorben, wobei die längste Überlebenszeit 42 Monate Betrug. Kranke, die mit Röntgenstrahlen behandelt wurden, lebten durchschnittlich 5.2 Monate im Vergleich zu 1.9 Monaten Überlebenszeit bei nicht behandelten Fällen. Bei den behandelten Patienten

wurden di Symptom z.T. oder zur Gänze behoben in 70%. Es wird gefolgert, dass die Strahlentherapie eine wertvolle Methode darstellt zur Behebung der Symptome bei inoperablen Lungencarzinom und gelegentlich eine Verlängerung des Lebens bewirken kann.

REFERENCES

1 Ariel, I. M.; Avery, E. E.; Kanter, L.; Head, J. R., and Langston, H. T.: "Primary Carcinoma of the Lung." *Cancer* 3:229, 1950.

2 Blenshard, G.: "The Palliation of Bronchial Carcinoma by Radiotherapy." *Lancet* 2:897, 1955.

3 Kutz, E. R.: "The Influence of Histologic Type on Survival Following Radiotherapy of Bronchogenic Carcinoma." *J. Thoracic Surg.* 32:165, 1956.

4 Schulz, M. D.: "The Results of Radiotherapy in Cancer of the Lung." *Radiology* 69:494, 1957.

5 Smithers, D. W.: "Carcinoma of the Bronchus; A Radiotherapy Viewpoint." *J. Fac. Radiologist* 6:174, 1955.

6 Watson, T. A.: "Supervoltage Roentgen Therapy in Cancer of the Lung." *Am. J. Roentgenol.* 75:525, 1956.

Resection for Pulmonary Tuberculosis in Infants and Children*

JOHN P. IGINI, M.D., F.C.C.P.,* ROBERT T. FOX, M.D., F.C.C.P.,** and WILLIAM M. LEES, M.D., F.C.C.P.***

Chicago, Illinois

The treatment of pulmonary tuberculosis in infants and children has been, until recently, entirely medical. Prior to 1949 pulmonary resection of tuberculous lesions in children was not widely attempted, although such procedures for bronchiectasis, cystic disease, etc. have been generally accepted. The advent of better surgical technique, endotracheal anesthesia, and better understanding of pre and postoperative care have given all types of intrathoracic surgery a satisfactory margin of safety in children. The introduction and intelligent use of the specific antituberculous drugs, especially streptomycin and isonicotinic acid hydrazide, has afforded great advances in the therapy of tuberculosis in general. More specifically, these drugs have aided in the resolution and clearing of pulmonary lesions to a point where surgical excision is feasible and, together with other antibiotics, have protected these children from the majority of infectious complications during the postoperative period.

The various surgical procedures commonly used in adult tuberculous patients could not be carried over entirely to the treatment of infants and children. It is common knowledge that thoracoplasty in young patients up to the age of 16 is usually contraindicated because of the incidence of severe scoliosis and resultant embarrassment of cardiorespiratory function. Pneumothorax has never been very satisfactory in young children, although pneumoperitoneum is tolerated fairly well by older children.

The medical literature in the past few years contains several reports on excisional surgery for pulmonary tuberculosis in infants and children. In 1950 Levitan and Zelman[1] reported four cases of pneumonectomy for tuberculosis, the patients ranging in age from two and one half to 12 years. Three of these were successful in achieving arrest of the disease. In 1952 Rubin and Mishkin of Seton Hospital, N. Y., reported on excisional surgery in 30 tuberculous children and adolescents, ranging from seven to 16 years in age There were two surgical deaths. A more recent report by Rubin, et al., has extended their series to 62, with four operative deaths (15 per cent).

We wish to outline our experience with resectional surgery in children at the Chicago Municipal Tuberculosis Sanitarium from 1949 through 1954. Fifteen years was arbitrarily selected as the upper age

---

†From the Department of Surgery, Municipal Tuberculosis Sanitarium.

*Formerly, Resident in Thoracic Surgery, Municipal Tuberculosis Sanitarium. Presently, Clinical Assistant, Department of Surgery, Stritch School of Medicine — Loyola University.

**Assistant Chief of Surgery, Municipal Tuberculosis Sanitarium and Associate in Surgery, Northwestern University Medical School.

***Chief of Surgery, Municipal Tuberculosis Sanitarium and Clinical Associate Professor in Surgery, Loyola University — Stritch School of Medicine and Mercy Hospital.

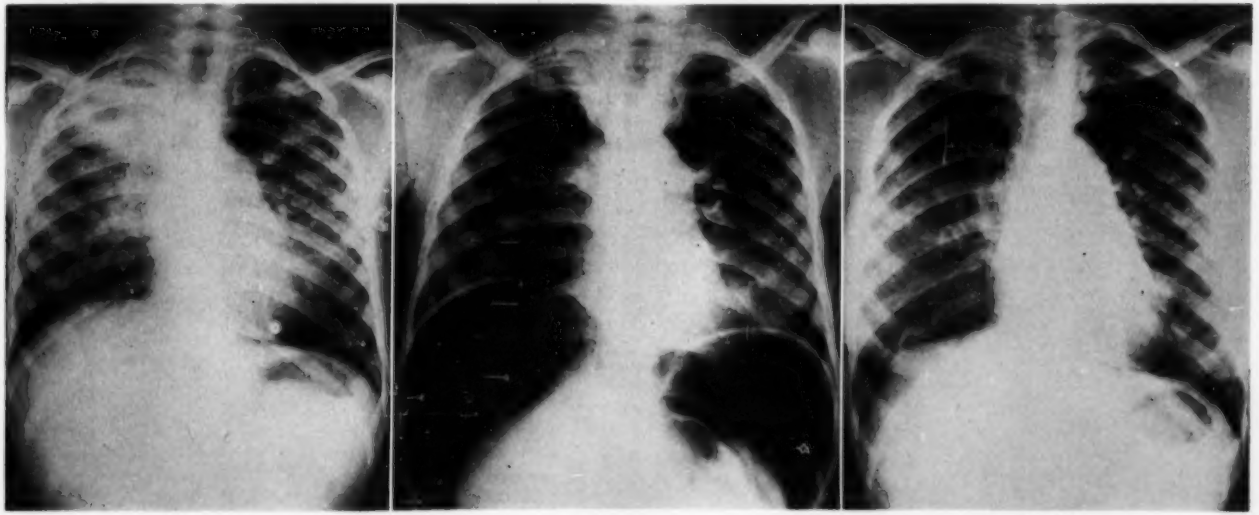


FIGURE 1 FIGURE 2 FIGURE 3

FIGURE 1. D.W.: Film taken after 90 days of antituberculous chemotherapy. Extensive bilateral disease still present.

FIGURE 2. D.W.: After 16 months of antimicrobial drugs and 12 months of pneumoperitoneum. The right upper lobe is destroyed and contracted. The remaining disease has regressed and is remaining stable.

FIGURE 3. D.W.: Film taken 13 months after operation. No active parenchymal disease is visible.

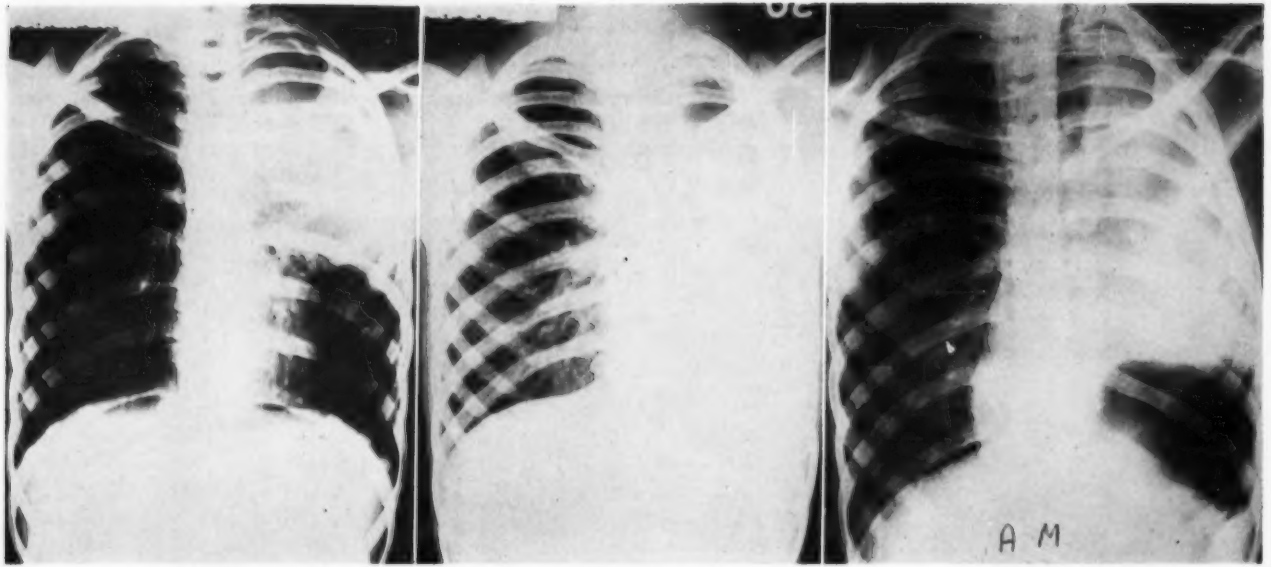


FIGURE 4 FIGURE 5 FIGURE 6

FIGURE 4. A.M.: Shortly after admission on June 27, 1949. Note extensive cavitation in the left apex with pneumonic infiltration beneath it and scattered nodular infiltration in left lower lung field and also in the right mid-lung field.

FIGURE 5. A.M.: Preoperative film. After 11 months of antimicrobial therapy there is still extensive residual cavitary disease in the left upper lung with a combination of nodular disease and atelectasis of the lower lobe secondary to the fibrostenosis of the bronchus.

FIGURE 6. A.M.: Chest film 2½ years after left pneumonectomy. Note elevation of left hemidiaphragm, heart in midline, and moderate retraction of superior mediastinal structures to the left. No eviednce of active parenchymal disease on the right is seen.

limit for this group, and we are presenting 25 cases, with an average age of 11 years and six months. The youngest was two years and nine months of age. There were four children five years or under, one child in the six to 10 year group, and 20 in the 11 to 15 year bracket. Of these, 22 were Negro and three White. Nineteen were girls and six were boys.

Fourteen of the 25 children had a history of immediate family contact and their disease was diagnosed by follow-up x-ray films of such contacts. Six of the 25 were asymptomatic, and of the remaining 19 with symptoms, 15 had an acute onset. The remaining four had an insidious beginning.

On reviewing the records, it was of interest to note the long period of time between the initiation of treatment and the performance of surgery. The shortest period between diagnosis and resection was 11 months, and the longest was five years, with an average of 27½ months. It is obvious that every effort was made to provide for maximum clearing of the disease prior to considering resectional surgery. In our earlier experience it was felt that surgery was to be reserved for the salvage type of case, but as satisfactory results were achieved a much more aggressive definitive attitude was taken.

The indications for resection in children are not as clear-cut as they are in adults. In addtion to the universally recognized indications as applied to children, there are the cases of progressive unilateral disease and the progressive primary complex. These are cases where, because of insufficient host resistance, intercurrent infection or nutritional deficiency spread of the lesion occurs. This progression occurs in the patients who fail to form a fibrous wall or capsule about the primary focus of infection. The spread occurs by contiguity or aspiration and soon the entire lobe or segment may become involved (Fig. 7). With continued progression liquefaction and cavitation appear (Fig. 4). From this progressive lesion, aspiration with rapidly progressing generalized tuber-

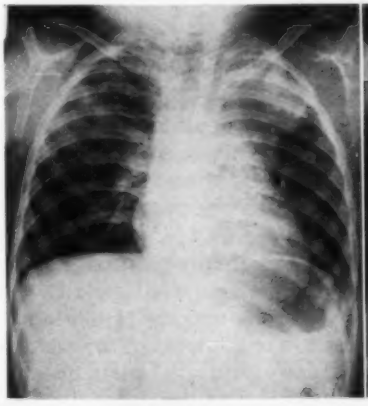


FIGURE 7

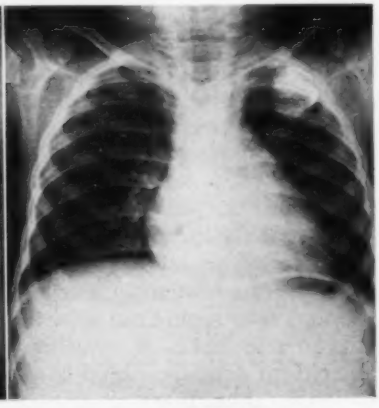


FIGURE 8

FIGURE 7. M. A.: Admission film, March 1952. Pneumonic lesion in left upper lobe and lesser infiltration in right upper lung field.

FIGURE 8. M. A.: Preoperative film, January 1954. Localized lesion in left upper lobe with stippling of calcium. Infiltrate on right has cleared.

culosis of the lungs may develop. While this type of lesion may arise in any portion of the lung, the lower lung fields are more frequently involved. These areas are, therefore, permanently and irrevocably damaged and constitute a continued hazard to the patient who harbors them. We, therefore, agree with Boyd and Wilkinson[7] that resection is to be advocated when such permanent damage seems inevitable.

Of the 25 patients, 19 had detectable disease on one side only, whereas six had bilateral involvement. In these latter cases, criteria for surgical consideration included evidence of stability of the contralateral lesions as demonstrated by serial x-ray films and, occasionally, by laminagraphic study. Fourteen of the total number had roentgenographic evidence of cavitation, three with associated atelectasis, one had a destroyed lung and one a tuberculoma. Four of the children had progressive primary disease.

Because the period of this study goes back to 1949, and since the presurgical treatment in these children ranged from 11 months to five years, the program of antibiotic and inflation collapse therapy was quite varied. Early in this period, short courses of chemotherapy consisting of streptomycin with or without PAS was given. The more recent group had long periods of treatment with dihydrostreptomycin (DHSM), para aminosalicylic acid (PAS), and isoniazid (INH). In all, six of the children had six months or less of chemotherapy, 10 from six months to a year, and nine had more than one year of chemotherapy. Nine of the 25 children had pneumoperitoneum for varying lengths of time, four had pneumothorax, three had temporary phrenic nerve interruptions, and one had had a extrapleural pneumothorax. It was felt that pneumoperitoneum had been of appreciable value in most of those cases in which it was used, whereas, the benefit from the other ancillary measures mentioned was doubtful. Extra-pulmonary tuberculosis was significant in one patient, a child who had had tuberculous meningitis and Pott's disease. These lesions were controlled before pulmonary surgery was considered.

A tracheobronchial tree grossly free of any tuberculous endobronchitis was a prerequisite for resection. All patients were bronchoscoped preoperatively. Six had endobronchitis necessitating postponement of surgery. These responded to increased dosage of streptomycin augmented with periods of aerosol inhalation of pencillin and streptomycin, so that subsequent bronchoscopic inspection demonstrated complete clearing of the endobronchitis. At the present time, streptomycin is used in place of dihydrostreptomycin.

There were 24 resections completed in the 25 children (Table 1). There were five pneumonectomies, four on the left, one on the right; 15 lobectomies, and four segmental resections. There is no case of bilateral resection. In one instance, resection was not completed. This was in a 15 year old girl who developed cardiac arrest during the hilar dissection for a contemplated pneumonectomy. Resuscitative measures, including rhythmic manual systole, were successful in re-establishing apparently normal cardiac action and the chest was promptly closed. The child expired about one hour later however, despite all further efforts. There was one other death. This occurred on the seventh postoperative day

TABLE 1 OPERATIVE PROCEDURES IN 25 PATIENTS

Segmental Resection	No. of Cases	No. of Operations
Apico-posterior of Left Upper Lobe	3	4
Basal of Left Lower Lobe	1	
Lobectomies		
Right Upper	7	15
Right Upper and Superior Segment of Right Lower Lobe	1	
Right Middle and Lower	2	
Right Middle	1	
Right Lower	1	
Left Upper	3	
Pneumonectomies		
Right	1	5
Left	4	
Thoracotomy, No resection		1

following left pneumonectomy in a 12 year old girl. Death was due to massive spread of the tuberculous infection into the contralateral lung. In this girl all sputum specimens were positive for tubercle bacilli despite seven months of dihydrostreptomycin.

Postoperative Complications

There were surprisingly few complications postoperatively. As reported in the literature previously, these young patients sometimes have a fear of deep breathing and coughing. Consequently, retained bronchial secretions may become a major problem. Our patients were cooperative. Preoperatively they were instructed to breathe deeply and cough, and they were even rehearsed. This proved beneficial in alleviating some of their fears. Tracheal aspiration was used on two or three occasions, and bronchoscopic aspiration of retained secretions was not necessary in any case.

As seen in Table II, there were two cases of contralateral spread. One ended in death, being very fulminating in nature. The other case was controlled by continuation of chemotherapy in the form of streptomycin and PAS. This second case of contralateral spread occurred in a 12 year old girl who had left pneumonectomy for large cavitary disease with scattered disease also in the right lung. She had positive sputum preoperatively and received just four months of streptomycin preoperatively. Her sputum was quickly converted and the disease came under control. She was discharged arrested 26 months postoperatively.

There was one case of tuberculous empyema following left basilar segmentectomy. This quickly cleared with repeated aspiration and chemotherapy. As noted, there was no bronchopleural fistula, wound infection, or other complication.

TABLE II POSTOPERATIVE COMPLICATIONS

Bronchopleural Fistula	0	
Empyema (closed) Tuberculous	1	
Contralateral Spread	2	(one fulminating resulting in death 7 days postoperatively)
Wound Infection	0	

Pathology

1. Preoperatively an attempt was made to predict the pathologic changes to be found in the diseased lung. This was based on the chronologic history of the patients, disease, and roentgenographic interpretation. The resected specimens were carefully studied and found to substantiate our preoperative impression in 21 of the 25 cases. (The autopsy specimen of the case of cardiac arrest was included). In the four cases in which our prediction was in error, instead of the expected cavitation, the specimen showed bronchiectasis or fibrocaseous disease alone. One specimen showed a thin-walled, cystic lesion with fibrous lining, showing no signs of gross or microscopic tuberculous disease. This was either an example of so-called "open healing," or else a cystic dilatation distal to tuberculous endobronchial disease. The above has shown that the preoperative impression may be expected to correlate closely with the disease demonstrated in the surgical specimen.

2. Essentially, the disease found in the surgical specimens may be classified as follows:

	Total
Fibrocaseous Tuberculosis with cavitation	11
Fibrocaseous Tuberculosis with calcification	5
Fibrocaseous Tuberculous foci	6
Tuberculous Bronchiectasis	1
Fibrosis with Cystic Formation	1
Fibrosis	1

In addition to the major changes described above, there was found varying degrees of involvement with bronchiectasis, atelectasis, fibrosis and endobronchitis.

Results

All patients to date have been discharged as arrested in the postoperative period which has varied from three to 24 months. All 23 surviving resectional surgery are living and well, and are free of any signs of active tuberculosis. All are pursuing normal physical activity.

These patients have been followed in the Clinic Division with repeated roentgenograms, sputum and gastric lavage cultures and have been found to be free of acid-fast organisms.

Case Reports

D. W. An 11½ year old colored girl admitted to M.T.S. on February 11, 1953, had insidious onset of disease. The admission x-ray film showed extensive bilateral disease; sputum was positive. After 90 days of chemotherapy in the form of streptomycin, isoniazid and PAS, she showed remarkable improvement, and pneumoperitoneum was initiated.

After 14 months therapy, cultures became negative; ther was further contraction of disease in the right apex. After 12 months of chemotherapy, she was reviewed at the Surgical Conference. She had atelectatic right upper lobe with some scattered lesions throughout both lung fields. On October 5, 1954 right upper lobectomy and superior segmentectomy was performed.

The pathologic report showed the right upper lobe to be the seat of many discrete and confluent fibrocaseous nodules measuring up to 1 cm. in diameter. In the superior segment of the lower lobe complete replacement by large fibrocaseous foci up to 2 cm. in diameter was noted. The caseous content could be easily evaluated.

She made an uneventful recovery and was given chemotherapy for 3½ months following surgery, and was discharged on January 29, 1955, being classified as inactive for the past 10 months. Follow-up questionaire indicates she is well and free of active disease.

A. M. A 12 year old colored girl admitted to sanitarium on June 27, 1949 after insidious onset of disease dating to March 1949, with diagnosis of primary tuberculosis. X-ray film showed dense pneumonic infiltration in the upper half of the left lung. She had 20 days of streptomycin before admission. This was continued for 60 days starting November 7, 1949. Bronchoscopic examination on July 13, 1949 was essentially negative. The surgical section reviewed the case and recommended left pneumonectomy on the basis of increased disease in the left lung, with the upper lobe entirely excavated and the lower lobe demonstrating consolidation. The right lung was free of demonstrable disease. Preoperative bronchoscopy showed no contraindication to surgery; however, a narrowing of the left main stem bronchus was noted. On June 2, 1950 left pneumonectomy was performed. This was complicated by contralateral spread in the right upper lobe. After this she was treated with dihydrostreptomycin and PAS, 12 gms. daily. After 90 days this lesion showed improvement. Chemotherapy was continued for 210 days. There was complete resolution of the right upper lobe spread by this time.

The resected lung showed a 3.5 cm. cavity in the upper portion surrounded by dense scar. The remaining portion of the lung showed numerous scattered caseous foci. A second cavity in the right upper lobe was 1.8 cm. in diameter and was filled with inspissated material.

Weight gain continued and sputum and stomach wash cultures were persistently negative. Last positive sputum was on April 9, 1951. On July 3, 1952 she was discharged as pulmonary tuberculosis, far advanced, inactive. She has been followed since discharge in the clinic division and found free of active disease, and carrying on normal school activities.

M. A. Admitted to the sanitarium in March 1952 at age of 19 months, by transfer from a private general hospital. He had an acute pneumonic onset in November 1951 with fever, chills and convulsions. Primary tuberculosis was diagnosed and he was treated with streptomycin and promizale at the private hospital. Figure VII shows the chest x-ray film in March 1952. Treatment at M.T.S. consisted of isoniazid, August 1952 to May 1954; PAS, May 1953 to May 1954; and Streptomycin, January 1954 to March 1954. On treatment the infiltrate on the right resolved and the lesion on the left slowly shrank to a circumscribed mass 3 cm. in diameter in the left upper lobe. This mass showed stippled calcification (Fig. VIII). All gastric and bronchial cultures were negative for acid-fast bacilli.

In January 1954 (age 3½ years) the residual lesion was removed by resection of the apico-posterior segment of the left upper lobe. The pathologist reported a 2 cm. caseous focus surrounded by dence scar and showing early calcification.

He was discharged as Inactive Primary Tuberculosis in June 1954 after a smooth convalescence.

Discussion

It is important to realize that both deaths and all but one of the complications occurred in the group of seven patients operated prior to 1953. This, of course, is attributed to the inadequate or interrupted chemotherapy in common usage at that time. In the 17 patients resected in 1953 and 1954, there was no mortality and only one complication, an empyema which responded promptly. There is no doubt that the determining factor in reducing the postoperative complications was the benefit obtained from adequate, long-term uninterrupted chemotherapy.

Children withstand surgery well and make rapid recoveries. They are more alert and less sensitive to pain; therefore, they cough and handle secretions better than adults. Their tolerance of anesthesia is better, they are soon ambulatory and the recovery period is shorter. Also, the resiliency of the lung tissue in children reduces the tendency to overdistension of the remaining lung as is often the problem encountered in adults. Children also withstand a greater loss of pulmonary tissue.

In review of this series it is obvious that the indication for pulmonary resection in children is essentially similar to that in adults, i.e., presence of significant fibrocaseous foci, with or without cavitation, persisting after an adequate period of uninterrupted chemotherapy.

SUMMARY

1. Twenty-five children ranging in age from two years and nine months to 15 years had excisional surgery for pulmonary tuberculosis.

2. There was one operative death, a cardiac arrest, and three postoperative complications, one resulting in death. This represents 8 per cent mortality.

3. All surviving patients are living and well, pursuing normal activity. No sign of active pulmonary disease was present within a 15 to 36 month follow-up period.

4. It has been demonstrated that pulmonary resection is a safe and effective mode of therapy for selected children with pulmonary tuberculosis.

Addendum: Since the end of 1954, 10 additional children in this age group have successfully undergone pulmonary resection without complication. There was no death. Therefore, the mortality figures may be revised as of this time to 2.9 per cent. A follow-up report from the out-patient clinic states that no difficulty has arisen in any of these children as of July 1, 1957.

RESUMEN

1. Se realizó cirugía de excisión en 25 niños de edades desde 2 años y 9 meses hasta 15 años, por tuberculosis pulmonar.
2. No hubo muertes operatorias, hubo un paro cardiaco y tres complicaciones postoperatorias, una de ellas motivo un fallecimiento.
3. Todos los que sobreviven están bien con actividad normal. No ha aparecido signo alguno de enfermedad activa dentro de un período de seguimiento de 15 a 26 meses.
4. Se ha demostrado que la resección pulmonar es un procedimiento seguro y efectivo en el tratamiento de casos escogidos de tuberculosis pulmonar en los niños.

RESUMÉ

1. Chez 25 enfants âges de 2 ans et 9 mois à 15 ans, on pratiqua une exérèse chirurgicale pour tuberculose pulmonaire.
2. Il y eut une mort opératoire, par arrêt cardiaque, et trois complications postopératoires, dont l'une se termina par la mort. Ceci représente un taux de mortalité de 8%.
3. Tous les malades survivants sont en bonne santé, poursuivant une activité normale. Il n'y eut aucun signe d'affection pulmonaire active pendant la période de contrôle allant de 15 à 36 mois.
4. Il est ainsi démontré que la résection pulmonaire est un moyen sans danger et efficace pour certains enfants atteints de tuberculose pulmonaire.

ZUSAMMENFASSUNG

1. Es wurden 25 Kinder im Alter zwischen 2 Jahren und 9 Monaten bis zu 15 Jahren wegen Lungentuberkulose mit Resektion behandelt.
2. Es kam zu einem operativen Todesfall, einem Herzstillstand und 3 postoperativen Komplikationen, davon eine mit tödlichem Ausgang. Somit betrug die Mortalität 8%.
3. Alle überlebenden Kranken sind wohlauf und führen ein normales Dasein. Innerhalb einer Nachbeobachtungszeit von 15 bis 36 Monaten fanden sich keine Anzeichen einer aktiven Lungenerkrankung.
4. Es liess sich zeigen, dass die Lungenresektion in ausgedehnten Fällen ein sicheres und wirksames Behandlungsverfahren darstellt für Kinder mit Lungentuberkulose.

REFERENCES

1 Baffes, T. C., and Potts, W. J.: "Pulmonary Resection in Infants and Children," *Ped. Clinic of No. Am.*, Aug. 1954, 709.

2 Levitin, M., and Zelman, M.: "Excisional Surg. Treatment of Pulmonary Tbc. in Children," *A.M.J. of Diseases Children*, 79:34, 1950.

3 Rubin M., and Mishkin, S.: "Resection for Pulmonary Tuberculosis in Children and Adolescents," *Surg. Gyn and OB.*, 95:751, 1952.

4 Botelho, G. H.; Chapchap, A.; Pereira, H. L. G., and Cordeiro, O. U., of San Paulo, Brazil, "Pneumonectomy in the Treatment of Tuberculosis in Children," *Dis. Chest*, 2:642, 1951.

5 Bremer, J. L.: "The Fate of the Remaining Lung Tissue after Lobectomy or Pneumonectomy," *IB 10*, 6:336, 1937.

6 Bairth, G.; Crawford, C., and Rudstrom, P.: "Pulm. Function after Pneumonectomy and Lobectomy," *J. Thoracic Surg.*, 16:492, 1947.

7 Boyd, G. L., and Wilkinson, F. R.: "Pulmonary Resection in Childhood Tuberculosis," *Dis. Chest*, 26:442-451, 1954.

The Clinical Recognition of Carbon Dioxide Intoxication*

RONALD J. O'REILLY, M.D.**
Los Angeles, California

Within the last century, man has escaped early death only to become increasingly susceptible to age and the cumulative small insults of daily existence. There has been a shift to the right on the spectrum of disease. The focus has been readjusted to include not only the acute, fulminating episode, but also the chronic, long-term state.

Chronic pulmonary disease exemplifies this trend and stands as an ever increasing problem of medical and socio-economic importance. Concomitant with the increasing prevalence of chronic pulmonary disease is the parallel need for a more thorough understanding of the basic pathophysiology, diagnosis and clinical management of such disorders. There is a real need for a universal appreciation of the primary and secondary manifestations of the chronic lung diseases.

Carbon dioxide intoxication emerges from this framework as a syndrome which *must* be familiar to every physician who treats long term pulmonary diseases. Yet, this symptom complex continues to pass unnoticed and untreated. For years its symptoms have been unknowingly intensified and the gravity of its course inadvertently increased by treatments of the uninformed.

There exists the challenge of making this syndrome known to every practicing physician, medical student and nurse. The cause is vital and contemporary. This challenge will prevail until carbon dioxide intoxication becomes routinely stressed in student and house staff education, until it becomes a part of our major medical and surgical texts, and until it becomes firmly established in the differential diagnosis of the comatose state.

It is the purpose then of this paper to review the syndrome of carbon dioxide intoxication with emphasis on its clinical manifestations and pathophysiology. Included is an original quantitative survey of this symptom complex in which all the reported cases of the major contributors are analyzed as a group. In addition, 11 unreported cases from the files of the Veterans Administration Hospital, Los Angeles, California, have been summarized by the author and are presented in this review.

Clinical Manifestations

Carbon dioxide intoxication is understood as a syndrome occurring in patients with poor pulmonary function, anoxemia, carbon dioxide retention, respiratory acidosis (which may or may not be compensated), and altered central and peripheral respiratory control. Thereafter, any factor or combination of factors which further compromises pulmonary gas exchange may lead to an additional accumulation of carbon dioxide and to an increased acidosis with the development of this distinct clinical entity.

*Second Prize, 1958 Essay Contest, American College of Chest Physicians.
**From the Veterans Administration Hospital and the Department of Radiology, University of California Medical Center.

TABLE 1 — UNDERLYING DISEASE PROCESSESS FROM 91 REPORTED CASES AND 11 NEW, UNREPORTED CASES

Diagnosis	Number Patients Literature	V. A. Series
1. Emphysema — alone or in combination with chronic bronchitis, pulmonary fibrosis, asthma or cor pulmonale	83	11
2. Asthma without chronic pulmonary disease	3	—
3. Restrictive thoracic cage disease, alone or in combination with #1 above	3	—
4. Tuberculosis — alone or in combination with thoracoplasty and/or pneumonectomy, or with #1 above	3	1
5. Primary cardiovascular disease	3	—
6. Carcinoma of the lung — alone or in combination with #1 above	2	—
7. Primary neurologic disease	2	—
8. Severe unilateral pleural thickening	1	—

Obstructive emphysema and pulmonary fibrosis constitute the most frequent pathological entities upon which carbon dioxide intoxication becomes superimposed (Table 1). Carbon dioxide intoxication may then be precipitated by the injudicious use of oxygen, pulmonary or tracheobronchial infection, congestive heart failure, sedative or narcotic drugs, bronchial asthma or surgery and anesthesia (Table 2). Occasionally this symptom complex will occur without underlying pulmonary disease, as in the respiratory depression of central nervous system trauma, bulbar polio and in cerebral vascular accidents.[8] Carbon dioxide intoxication has occurred without demonstrable precipitating cause.

The symptoms and signs of carbon dioxide intoxication are primarily neurological and chiefly involve impairment in the level of consciousness ranging from drowsiness and confusion to deep coma (Table 3). Likewise various psychologic changes may occur either as the sole manifestation of carbon dioxide intoxication or early in the course of consciousness impairment. Irritability and management problems, depression, hallucinations, hypomania, euphoria, and paranoid ideas have been reported.

Muscle twitching and fine tremors of the extremities or face are the most frequent motor signs.[6,8,12,13] Neuromuscular discharge phenomenon in the form of myoclonus and generalized convulsions are also possible.[4,6,12,13] Extremity paralysis may be flaccid or spastic.[8,12]

Reflex changes when present consist of absent or diminished or unequal deep tendon reflexes.[8,12,13] The corneal reflex may be lost in deep coma.[8,12] The pupils may be widely dilated or small and contracted. They may be unequal and react sluggishly to light.[8,12,13]

TABLE 2 — PRECIPITATING FACTORS FROM 103 REPORTED CASES AND 11 NEW UNREPORTED CASES

Factor (alone or in part responsible)	Number of Instances Literature	V. A. Series
Oxygen	69	5
Infection	34	6
Congestive Heart Failure	41	4
Acute asthma or status asthmaticus	8	—
Drug depression	15	—
Post-operation	4	—
Pleural effusion	1	1

Fundascopic examination may reveal papilledema and/or dark, dilated retinal veins.[9,10,13]

Increased intercranial pressure (probably accounting for the papilledema) may accompany carbon dioxide intoxication and originally was offered as a possible etiological factor in symptom production. It is now generally felt, however, that the increased pressure is secondary to the vasodilatory effects of hypercapnia, anoxia and acidosis. The pressure change is an associated phenomenon, not the cause, of the central nervous system symptoms.[9,13]

Specific cranial nerve (except II), sensory or cerebellar signs have not been described.

The non-neurologic signs and symptoms of carbon dioxide intoxication are predominantly cardiopulmonary. Respiratory depression is evident, varying from mild ventilatory depression to frank apnea. Cyanosis is always present when the patient is breathing room air. There may be an increase in blood pressure.[13] Sieker, however, stresses the important complication of hypotension and shock which may occur after a period of induced hypertension.[5] Experience at the Veterans Hospital corroborates this finding of severe circulatory collapse unresponsive to extensive vasopressure therapy. Warm, flushed skin with excessive perspiration is not uncommon.[4,5,13] Tachycardia is frequent.[5]

TABLE 3 — REPORTED NFUROLOGIC MANIFESTATIONS FROM 119 CASES AND 11 NEW, UNREPORTED CASES

Symptom or Sign	Total Number of Patients Exhibiting the Finding At Least Once	
	Literature	V. A. Series
Impairment of Consciousness		
Drowsy or confused — only	33	4
Stupor or semicoma — only	15	4
Coma — eventual	48	2
Psychologic Changes		
Depression	1	
Irritability and management problems	13	
Hallucinations	2	
Hypomania	1	
Paranoid ideas	1	
Euphoria	1	
Motor Phenomenum		
Twitching or tremor	8	1
Myoclonus	4	
Generalized convulsions	1	1
Paralysis	5	
Reflex Changes		
Hypoactive or unequal	3	1
Absent	4	1
Optic Changes		
Papilledema	11	
Dilated pupils	1	
Contracted pupils	2	
Unequal or sluggish reacting pupils	6	2
Cerebral Spinal Fluid		
Increased pressure	5	

Pathophysiology

Carbon dioxide retention and arterial anoxia provide direct evidence of abnormal pulmonary physiology, inadequate gas exchange, and ineffective compensation. The defects in blood gas homeostasis result from hypoventilation and from marked regional variation in the ratio of alveolar ventilation to pulmonary capillary blood flow.[3] Abnormal ventilation-perfusion ratios produce additional anatomic dead space and prevent full oxygenation and CO_2 depletion of pulmonary capillary blood. If a sufficient number of well ventilated and perfused alveoli remain, hyperventilation can prevent carbon dioxide retention. Anoxemia, however, always occurs with low ventilation-perfusion ratios.[3]

Respiratory acidosis is the biochemical result of carbon dioxide retention. Metabolic compensation occurs by way of the whole body buffers, the renal secretion of an acid urine, ammonia excretion and the increased tubular resorption of bicarbonate.[5] Uncompensated respiratory acidosis exists chronically when pulmonary function is unable to maintain the concentration of carbonic acid at a level below the maximum 'acid-accepting capacity' or it exists acutely when pulmonary ventilation fails.[1,5]

Ventilation is regulated centrally and peripherally in a manner whereby respiratory depression is counteracted by the resultant stimulant effects of increased pCO_2, increased hydrogen ion concentration, and decreased pO_2. Normally, respiration is finely controlled by minute changes in blood pCO_2. A decrease in blood pH per se is thought to act as a central respiratory stimulant. The central depressant effects of hypoxia are overcome when arterial oxygen saturation falls to 90-95 per cent and respiration becomes driven reflexly by impulses originating in the aortic and carotid bodies. These three mechanisms act jointly in producing the compensatory hyperventilation seen in certain patients with chronic pulmonary disease, but they are obviously ineffective in those patients who hypoventilate in the face of abnormal blood gases and diminished pH.

Patients with emphysema exhibit a diminished respiratory response to the inhalation of carbon dioxide. It is now the general feeling that, although abnormal respiratory mechanics may play a role, the prime factor is an actual refractiveness of the medullary center to increases in pCO_2.[1,7,8]

Chemoreceptor regulation becomes increasingly important as the respiratory response to hypercapnia diminishes. Anoxia often becomes the primary respiratory stimulant and any effort to correct the low blood oxygen results in severe depression of respiration, hypercapnia and acidosis.

The injudicious use of oxygen in patients with chronic pulmonary disease is an event of prime clinical importance in the precipitation of carbon dioxide intoxication. The response to oxygen is variable as to degree of respiratory depression and time of symptom development. Acute apnea is possible though the respiratory depression is usually less remarkable. Symptoms may develop insidiously or may quickly appear a few minutes after institution of oxygen therapy. Certain patients

appear symptom free for long periods of time before ventilation suddenly fails and carbon dioxide intoxication becomes obvious.[8]

In the majority of reported cases, carbon dioxide intoxication developed during hospitalization. This finding amplifies the importance of very careful management and underlines the necessity for alerting all hospital personnel to the possibility of symptom development in patients with chronic pulmonary disease — particularly after the institution of oxygen therapy. Vigilant nursing care is invaluable and many times the 'oft' forgotten nursing notes provide the first recorded symptoms of carbon dioxide intoxication. But, it is the physician who accepts ultimate responsibility for oxygen therapy. He must specify the exact concentration, route, flow rate and administration time and must be in attendance during the first critical 15 to 30 minutes of oxygen administration to every new patient with chronic pulmonary disease.

Oxygen is vital in the management of certain phases of chronic pulmonary disease; and in no way is it meant to imply that oxygen therapy is contraindicated in these patients. Significant changes in ventilation and blood gases are not always seen following institution of oxygen therapy and the majority of patients with chronic hypoxia do not develop carbon dioxide intoxication when oxygen is given.[9,13] In general, the most constant and profound changes in ventilation can be expected in those patients with particularly low initial oxygen saturation[2]. Therefore, the most worthy candidates for oxygen therapy are the greatest risks for oxygen induced respiratory depression.[2]

Pulmonary and tracheobronchial infections frequently precipitate carbon dioxide intoxication. The mental changes of carbon dioxide intoxication may serve as the first sign of acute infection in the patient with chronic lung disease. Impairment of gas exchange results from the deleterious effects of inflammation on ventilation, e.g. increased bronchiospasm, mucous membrane edema, increased secretions, etc.[8] These factors are additive in the production of deeper anoxia, further carbon dioxide retention and acute respiratory acidosis.

Congestive heart failure is a frequent coexistent of carbon dioxide intoxication. This relationship stems from the role of pulmonary parenchymal disease in the etiology of cor pulmonale. In turn, cardiac decompensation can precipitate carbon dioxide intoxication. This latter relationship results in part from the deleterious effects of congestive heart failure on pulmonary function and in part from the increase in cellular pCO_2 and H^+ secondary to a failing peripheral circulation.

Narcotic and sedative drugs (particularly the barbiturates and morphine) can act individually or in combination with other factors to precipitate carbon dioxide intoxication.[1] The care which must be taken in administering these drugs to patients with chronic pulmonary disease cannot be overemphasized.

There is no unity of opinion regarding the relative roles of hypercapnia and acidosis in the production of carbon dioxide intoxication. Evidence is lacking which definitely points to one of these factors as the prime etiological agent.

As so often is the case, the final analysis may reveal that hypercapnia and acidosis act together in symptom production and that neither is the

exclusive factor. Westlake[13] offers a good working hypothesis — namely, that the central nervous system is sensitive to high levels of carbon dioxide and acidosis, but can adapt to hypercapnia in the face of normal pH. However, there is probably a threshold for pCO_2 above which further elevations in blood gas produce symptoms regardless of hydrogen ion concentration.

A review of the literature of carbon dioxide intoxication failed to reveal reference to specific gross or microscopic pathologic findings in the central nervous system. Probably the major pathological changes are biochemical and reflect changes in the gaseous and acid environments of intracellular enzyme systems.[13]

Diagnosis

Arterial pH and pCO_2 constitute the evidence upon which the diagnosis of carbon dioxide intoxication is ultimately based.[6] In actual practice, however, the determination of arterial pCO_2 is time consuming and is an impractical procedure for the busy hospital admitting officer or ward physician. pH measurements are rapid and accurate. For all practical purposes, carbon dioxide intoxication can be diagnosed on the basis of its accompanying respiratory acidosis.

No definite levels of arterial pH or pCO_2 have been set as diagnostic. Table 4 summarizes a compilation of 58 cases from eight separate series where clinical symptoms were correlated with levels of arterial pCO_2 and pH. The wide range of values and the large overlap between these values and the level of consciousness probably result from variation in individual susceptability and rate of symptom development.

Patient response to a 'test dose' of oxygen[11] is a simple, yet unpublished, diagnostic procedure. Deepening narcosis, secondary to oxygen administration, is good evidence in favor of the syndrome. The oxygen provacative test may prove to be one of the most useful procedures in the diagnosis of carbon dioxide intoxication.

Cerebral vascular disorders merit primary consideration in the differential diagnosis of this syndrome. Diabetic acidosis, electrolyte disturbance, hepatic coma and uremia must be ruled out. The usual signs and symptoms of severe non-pulmonary infection and septicemia may be masked in these older patients and a disturbance in consciousness may be the only presenting finding. The hospital admitting officer must add central nervous system trauma and the primary toxic effects of alcohol or drugs to his list of diagnostic possibilities.

A careful history and physical examination are fundamental to the diagnosis of carbon dioxide intoxication. Special reference must be

TABLE 4 — CORRELATION BETWEEN ARTERIAL pCO_2 AND pH AND LEVEL OF CONSCIOUSNESS FROM 58 REPORTED CASES

Level of Consciousness	Range pCO_2 (mm. Hg.)	pH	Mean pCO_2 (mm. Hg.)	pH
Coma	69—228	6.83—7.40	129±7.1	7.09±.03
Semicoma	76—140	7.12—7.38	103±4.8	7.20±.02
Drowsy	52—93	7.19—7.38	80±4.8	7.27±.02

made to the neurological examination — particularly to the presence or absence of localizing signs and the character of the spinal fluid. A detailed evaluation of the cardiopulmonary status is essential.

SUMMARY AND CONCLUSION

Carbon dioxide intoxication has been presented as a syndrome occurring primarily in patients with chronic pulmonary disease. When the injudicious use of oxygen, pulmonary infection, congestive heart failure or depressant drugs further compromise pulmonary function, the neurological and cardio-pulmonary symptoms and signs of carbon dioxide intoxication become manifest. Attention has been called to the care which must tbe taken in the administration of oxygen and depressant drugs to patients with chronic pulmonary disease and to the importance of adding carbon dioxide intoxication to the differential diagnosis of the comatose state.

ACKNOWLEDGMENT: I gratefully acknowledge the advice and encouragement of Daniel H .Simmons, M.D., Ph.D., of the Department of Internal Medicine, Veterans Administration Hospital, Los Angeles; and Bernard J. O'Loughlin, M.D., Ph.D., of the Department of Radiology, University of California, Los Angeles.

RESUMEN

La intoxicación por el bióxido de carbono se ha presentado como un síndrome que ocurre primariamente en los enfermos con afección pulmonar crónica.

Cuando se hace uso no juicioso del oxígeno, o hay infección pulmonar, insuficiencia cardiaca congestiva o se usan drogas depresoras se daña más la función pulmonar y aparecen manifiestamente los signos de intoxicación por el anhodrido carbónico.

Se llama la atención sobre el cuidado que debe tenerse al administrar el oxígeno y las drogas depresora a enfermos con enfermedad pulmonar crónica y sobre la importancia que tiene el agregar la intoxicación por el bióxido de carbono en el diagnóstico diferencial en el estado comatoso.

RESUMÉ

L'intoxication par le gaz carbonique a été présentée comme un syndrome survenant principalement chez des malades atteints d'affection pulmonaire chronique. Quand un emploi intempestif d'oxygène, une infection pulmonaire, une crise cardiaque ou des médications dépressives compromettent ultérieurement la fonction pulmonaire, les symptômes neurologiques et cardiopulmonaires et les signes d'une intoxication par le gaz carbonique deviennent manifestes. On doit appeler l'attention sur le soin avec lequel doivent être administrés l'oxygène et les médications dépressives chez les malades atteints d'affection pulmonaire chronique. Il est important enfin d'ajouter l'intoxication par le gaz carbonique dans le diagnostic différentiel des états comateux.

ZUSAMMENFASSUNG

Darstellung der CO_2-Vergiftung als eines Syndroms, das in erster Linie bei Kranken mit chronischen Lungenerkrankungen auftritt. Beeinträchtigt der unüberlegte Einsatz von Sauerstoff oder eine pulmonale Infektion oder eine Herzinsuffizienz mit Stauung oder Beruhigungsmittel zusätzlich die Lungenfunktion, werden die neurologischen und cardio pulmonalen Symptome und Zeichen der CO_2-Vergiftung offenbar. Aufmerksamkeit wurde auf die Sorgfalt gelenkt, die man beim Gebrauch von CO_2 und Beruhigungsmittel bei Kranken mit chronischen Lungenkrankheiten wahrnehmen muss, und auf die Wichtigkeit, bei der Differentialdiagnose eines komatösen Zustandes auf die CO_2-Vergiftung einzubeziehen.

REFERENCES

1 Cohn, J. E.; Carroll, D. E., and Riley, R. L.: "Respiratory Acidosis in Patients with Emphysema," *Am. J. Med.*, 17:447, 1954.

2 Comroe, J. H., Jr.; Bahnson, E. R., and Coates, E. O., Jr.: "Mental Changes Occurring in Chronically Anoxemic Patients During Oxygen Therapy," *JAMA*, 143:1044, 1950.

3 Comroe, J. H., Jr.: Forster, R. E. II; DuBois, A. B.; Briscoe, W. A., and Carlsen, E.: "The Lung-Clinical Physiology and Pulmonary Function Tests." *The Year Book Publishers, Inc.*, Chicago, 1955.

4 Davis, C. E., and Mackinnon, J.: "Neurological Effects of Oxygen in Chronic Cor Pulmonale," *Lancet*. 257:833, 1949.

5 Moore, F. D.: "Common Patterns of Water and Electrolyte Changes in Injury, Surgery and Disease (Continued)," *New Eng. J. Med.*, 258:377, 1958.

6 Pare, J. A. P.; Morton, J. W., and Rose, B.: "Carbon Dioxide Narcosis and the Management of Advanced Pulmonary Insufficiency," *Canad. M. A. J.*, 73:278, 1955.

7 Prime, F. J., and Westlake, E. K.: "The Respiratory Responses to Carbon Dioxide in Emphysema," *Clin. Sci.*, 13:321, 1954.

8 Sieker, H. O., and Hickam, J. B.: "Carbon Dioxide Intoxication — The Clinical Syndrome, its Etiology and Management, with Particular Reference to the Use of Mechanical Respirators," *Med.*, 35(4):389, 1956.

9 Simpson, T.: "Papilledema in Emphysema," *Brit. M. J.*, 2:639, 1948.

10 Simpson, T.: "Acute Respiratory Infections in Emphysema," *Brit. M. J.*, 1:297, 1954.

11 Simmons, D. H.: Personal Communication.

12 Veterans Administration Hospital, Los Angeles, California.

13 Westlake, E. K.; Simpson, T., and Kaye, M.: "Carbon Dioxide Narcosis in Emphysema," *Q. J. Med.*, 24:155, 1955.

Bronchography Using Dyclonine Hydrochloride* Anesthesia

(*4 N-butoxy-beta-piperidino-propiophenone-hydrochloride)

DAVID E. WHEELER, M. D.
Indianapolis, Indiana

The recent ban on the use of tetracaine hydrochloride and cocaine hydrochloride as topical anesthetics in Veteran's Administration installations forced the use of other agents for anesthetization of the tracheobronchial tree prior to bronchography. Several different drugs were tried before a relatively new agent, dyclonine hydrochloride ("Dyclone," Pitman-Moore) was investigated. This drug has been used exclusively for anesthesia in bronchography for the past two years. It is a topical anesthetic which is said to have a wide margin of safety, good anesthetic properties, and a low sensitizing potential.[1] The drug is an organic ketone, not one of the "caines" (esters), amides, or ethers.[2] A sterile 0.5 per cent solution with chlorobutanol in isotonic sodium chloride is used.

The technique of bronchographic examination presently used at this institution has evolved through several stages during the period of this series. Mapping following bronchoscopy has been abandoned completely, chiefly because of the time lag that occurs in transferring patients from surgery to x-ray with attendant loss of good anesthesia. Also, it seemed unnecessary to examine each patient with the bronchoscope before each bronchography. There has been no change in the pre-anesthetic administration of drugs, standard procedure consisting of the administration of pentobarbital and atropine according to body weight one to two hours before the procedure. A trial group of patients was given no pre-anesthesia and no untoward effects were noted. The meal immediately preceding the examination is always withheld.

The original procedure for administering anesthesia to the tracheobronchial tree in the x-ray department entailed spraying the oropharynx (a method first found extremely valuable in our hands as a preliminary to indirect laryngoscopy in patients with hypopharyngeal or laryngeal cancer), placing anesthetic-soaked cotton pledgets in the pyriform sinuses, and directly anesthetizing the trachea by instillation of anesthetic through a curved cannula, this method being similar to that described by Hughes, et al.,[3] in a report of 569 peroral endoscopies. Not infrequently as much as six ounces of the anesthetic was used. Much of this was expectorated or thrown away with the soaked pledgets, and a considerable amount was swallowed. An average of about 4 cc. and no more than a total of 6 cc. in aliquots of 2 to 3 cc. was instilled directly into the trachea. Subsequently, gargling of the anesthetic replaced the use of both the soaked pledgets and the spray, the patient being instructed to swallow the last ½ ounce. This method reduced the total amount of drug actually ingested, but much still was wasted in the expectoration cup.

It was noted that occasional accidental aspiration of part of the gargled anesthetic rendered the direct endotracheal instillation unnecessary. This fact suggested the method of producing anesthesia, used in recent months, by which the patient now receives spray alone as the complete procedure. He is instructed to inspire deeply during the spraying, and the atomized Dyclone gives excellent anesthesia of the oropharynx, hypopharynx, trachea, carina, and major bronchi. The total amount of anesthetic solution used averages 10 cc. and never exceeds 20 cc. Some of this is expectorated and a small amount is swallowed. The time consumed for an average examination is 20 minutes or less. The patients can eat or drink with safety in less than one hour.

The spray usually is administered by means of an ordinary hand atomizer. While power spray equipment makes the procedure faster and easier, and ordinarily uses less anesthetic, it is no more efficacious. However, the author has been prompted to suggest the marketing of Dyclone in pressurized "aerosol" cans as a means of providing adequate, simple, easily available "power" spraying. Attempts at spraying the contrast media, itself, have so far met with failure, but successful atomization of both the anesthetic and the contrast material (different compounds than those presently used) has been reported.[4]

Intubation of the trachea with red rubber catheter has been discarded in favor of a simpler and more effective method. After appropriate prepositioning of the patient, the radiopaque bronchographic medium is instilled (through a 30 cc. syringe fitted with adapter tip) into the trachea over the back of the tongue which is hyperextended. Vickers[5] gives credit to Lian, Darbois and Navarre (1922) for the first supraglottic instillation of material into the tracheobronchial tree, and he has compiled a list of advantages of this method, which will not be reviewed here. Since its use was eliminated, a tracheal catheter has been found not to be necessary for the satisfactory completion of the examination.

Dyclone has been used in the tracheobronchial tree of each of 69 patients prior to bronchographic mapping with propyliodone in oil suspension. In several instances more than one examination was made on the same patient, so that 121 actual instillations are represented by this group. Although unilateral examinations seem still to be preferred generally, the bilateral procedure has been successful here. In the 121 examinations, 92 bronchograms were satisfactory and 29 were unsatisfactory. A little more than one-half (16) of the 29 initial failures seemed to be directly attributable to poor anesthesia. In 13 of these patients examinations were repeated, with all but one being subsequently successfully anesthetized. This patient seemed to be a true example of resistance to the anesthetic properties of the drug, since he later was readily anesthetized with a different agent. The training program in progress at this hospital undoubtedly contributes to the number of initial by residents unfamiliar with bronchographic technique.
failures, but the simplified procedure outlined above is quickly mastered

SUMMARY

Dyclone has been found to be short-acting, safe, easy to administer, and effective as an agent for anesthetizing the tracheobronchial tree prior to bronchography. No patient was observed to suffer any adverse effect from the drug. One patient was resistant to repeated applications of the agent. The technique of application of

both anesthetic and contrast media has been simplified as much as possible, resulting in a saving of time for the radiologist, diminished morbidity for the patient, and improved studies for the clinician.

ACKNOWLEDGMENT: The author is indebted to Doctors Paul C. Harding and David C. Gastineau for editing and innumerable helpful suggestions.

RESUMEN

Se ha encontrado que el Dyclone as un anestésico para el árbol tráqueo-brónquico, de acción corta, segura, fácil de administrar y efectiva para usarse antes de la broncografía. Ningún enfermo tuvo resultados adversos. Un enfermo fué resistente a las aplicaciones reiteradas del agente. La técnica de aplicación tanto del anestésico como del material de contraste, se ha simplificado tanto como es posible con lo que resultó un ahorro de tiempo para el radiólogo con morbilidad disminuída para el enfermo y mejoría del estudio para el clínico.

RESUMÉ

L'auteur a constaté que le "dyclone" était un produit agissant rapidement, sans danger, facile à administrer, et efficace pour l'anesthésie de l'arbre trachéo-bronchique avant bronchographie. Il n'observa pas de malade souffrant d'effets secondaires de la médication. Un malade fut résistant à des applications répétées de ce produit. La technique d'application, à la fois de l'anesthésique et du milieu de contraste a été autant que possible simplifiée, et a permis un gain de temps pour le radiologiste, une diminution de la morbidité pour les malades et une amélioration des documents pour le médecin.

ZUSAMMENFASSUNG

Dyclon erwies sich als eine rasch wirksame, sichere, leicht anwendbare und effektive Substanz zur Anästhesie des Tracheabronchialbaumes bei der Bronchographie. Es wurde kein Fall bemerkt, der an irgend einem unerwünschten Effekt durch das Mittel gelitten hätte. Ein Kranker war resistent bei wiederholter Anwendung des Stoffes.

Die Technik der Anwendung-sowohl des Anästheticums als auch des Kontrastmittels-wurde soweit wie irgend möglich vereinfacht; dies begünstigt eine Zeitersparnis für den Röntgenologen, eine Herabsetzung der Morbidität für den Patienten und eine Verbesserung in der Untersuchung für den Kliniker.

REFERENCES

1 Harris, L. C.; Parry, J. C., and Greifenstein, F. E.: "Dyclonine — A New Local Anesthetic Agent: Clinical Evaluation," *Anesthesiology* 17:648, 1956.

2 Shelmire, B.; Gastineau, F. M., and Shields, T. L.: "Evaluation of a New Topical Anesthetic, Dyclonine Hydrochloride," *A.M.A. Arch. Dermat.* 71:728, 1955.

3 Hughes, F. A.; Burwell, J. R., and Pate, J. W.: "Use of a New Topical Anesthetic Agent (Dyclone) in Peroral Endoscopy," *J. Thoracic Surg.* 32:135, 1956.

4 Fariñas, P. L.: "Bronchography by Atomization," *Radiology* 51:491, 1948.

5 Vickers, A. A.: "Bronchography — The Methods by Which It May Be Performed and the Factors Influencing the Choice of Method Employed," *Brit. J. Radiol.* 22:137, 1949.

Catalase Activity as Variable Property of Mycobacteria*

G. FAHR, M.D., F.C.C.P., A. PUKITE, B.Sc., and E. DARZINS, M.D.
Anoka, Minnesota

The catalase activity of tubercle bacilli was detected by Hahn (1897). It came into focus of attention after Middlebrook's observation (1954) that tubercle bacilli of decreased pathogenicity, resistant to isoniazid, are devoid of catalase activity, which seemed to suggest that there might be a relation between catalase activity and pathogenicity.

A few authors have supported the claim of Middlebrook (Neumayr *et al.*, 1955; Meissner and Bonicke, 1957). In most cases the observations were controversial (Peizer and Widelock, 1955; Wolinsky *et al.*, 1956; Desbordes *et al.*, 1956), or no relation between catalase activity and pathogenicity was found (Stief and Hall, 1956; Takahashi, 1956; Besta *et al.*, 1957).

Differences in the technique of catalase determination, variability of the strains investigated, and environmental conditions may influence catalase activity.

The early authors in their investigation of catalase activity used the simple technique of suspending tubercle bacilli in peroxide solution and observing the amount of oxygen bubbles that appeared (Middlebrook, Desbordes and others). Some used Warburg's manometric technique (Fujita and Kodama, 1931; Finlayson and Edson, 1947; Desbordes *et al.*, 1956).

Material and Method

Catalase activity of three species of mycobacteria was studied under standardized conditions. *M.phlei, M.giae, and M.agua* were grown in Darzins' basal medium containing 0.5 per cent albumin fraction V, and 0.03 per cent Tween 80; the pH of the medium was 7.0. Erlenmeyer flasks (Pyrex) of 250 ml. capacity containing 50 ml. of medium were inoculated with 40μ g. of bacilli (dry weight) of a 24 hour old culture grown at 37°C. To investigate catalase activity two methods were used in parallel series. In Warburg's manometric technique the cultures were diluted to the same optical density, which was determined in an Evelyn photometer with filter transmitting 540μ wavelength. The dry weight of bacilli in these suspensions was determined. The manometers were read after 30 minutes, the temperature was 25°C; 0.5 ml. of 0.2 M peroxide solution was added to the suspension of 100μ g. of bacilli in 3 ml. of liquid in Warburg's vessels. The center well contained 0.2 ml. of 10 per cent potassium hydroxide solution. In another series of experiments iodometric titration of peroxide according to Stern (1932) was performed. In these titrations 10 ml. of undiluted culture was added to 20 ml. of buffered (pH 7.0) peroxide solution of not over 0.02 M strength, and titration was performed under exact observation of the time and temperature factors.

*Research Laboratory, Anoka State Hospital.

The action of carbon dioxide on catalase activity was investigated by dividing 24 hour old culture into three parts. In one series of flasks carbon dioxide in concentrations ranging from 5 to 100 per cent was passed over the cultures, the filled flasks were held at 37°C. for 2, 24, and 48 hours, and the catalase activity of the bacilli was measured. In another series nitrogen was used instead of carbon dioxide. The third series of flasks were cultured in air and served as controls. All experiments were performed twice.

Two different colonies were grown from the cultures of *M. phlei*. One variant was composed of small, smooth colonies, the colonies of other variant were large, rough.

Results

In more than 200 estimates, the course of peroxide splitting determined by means of titration method was more exact and less time-consuming than the manometric method; in addition to this the multiplication error was smaller in the titration method. The results obtained showed that the peroxide-splitting power is the particular property of each species or variant of mycobacteria. In *M. phlei* culture, maximum catalase activity was reached in the first 24 hours, when in 30 min. at 25°C. one mg. of bacilli (dry weight) decomposed 286 ± 14 micromoles of peroxide. In the culture of 48 hours the catalase activity was down to 176 ± 18 micromoles. In *M. giae* the activity increased slowly and reached its maximum between 48 and 72 hours, when in 30 minutes at 25°C. 150 ± 20 micromoles were split. *M.agua* showed increasing catalase activity in the first 24 hours, after that time it remained on the same level, when it decomposed 84 ± 9 micromoles of peroxide.

The smooth variant of *M.phlei* decomposed 23 ± 3 micromoles of peroxide, the rough variant decomposed 222 ± 17 micromoles.

The growth rate of investigated mycobacteria, determined by increase in turbidity of media and verified by colony count on serum agar, and their catalase activity, did not follow each other. The greatest growth rate was shown by *M.agua*, although its catalase activity was inferior to that of *M. phlei* and *M. giae*.

Under the action of carbon dioxide a considerable decrease in catalase activity occurred in all three species. After 24 hours under 100 per cent carbon dioxide concentration the catalase activity of *M. phlei* had the intensity of 114 ± 11 micromoles, in the next 24 hours it went down to 67 ± 10 micromoles; in *M. giae* it was 114 ± 16 micromoles, and 84 ± 14 micromoles; in *M. agua* 58 ± 8 and 48 ± 9 micromoles respectively.

Under nitrogen catalase activity in *M.phlei* decreased slightly, in *M.giae* and *M.agua* remained unchanged.

The drop in pH of cultures under carbon dioxide was from 7.0 to 6.5; parallel cultures grown in air at pH 6.5 did not show any significant drop in catalase activity. Decrease in catalase activity was roughly parallel to the carbon dioxide concentration in the atmosphere over the cultures.

SUMMARY

In the three species and two variants of mycobacteria investigated under standard conditions, catalase activity was variable.

Catalase activity was a particular property of each species or variant of mycobacteria investigated.

Catalase activity in the species investigated was not directly related to their rate of growth.

Carbon dioxide had a depressing effect on catalase activity; at 100 per cent concentration in the atmosphere, catalase activity was reduced in 48 hours by approximately 50 per cent. Nitrogen did not have such an effect.

RESUMEN

En las tres especies y dos variantes de micobacteria estudiadas bajo condiciones estandar, la actividad de la catalasa fué variable.

La actividad de la catalasa fué una propiedad particular de cada especie o variante de micobacteria investigada.

La actividad de la catalasa en las especies investigadas no estaba directamente en relación con su proporción de crecimiento.

En bióxido de carbono tuvo un efecto depresor en la actividad catalásica; a la concentración de 100 por ciento en la atmósfera la actividad catalásica re redujo en 48 horas aproximadamente un 50 por ciento. El nitrógeno no tuvo tal efecto.

RESUMÉ

Dans les trois types et deux variantes de mycobacterium examinés dans des conditions standard, la catalase se montra variable.

La catalase fut une caractéristique particulière de chaque type ou variété de bacilles examinés.

La catalase du type de bacille examiné ne fut pas directement lieée à leur possibilité de culture.

Le gaz carbonique a un effet inhibiteur sur la catalase. Au taux de 100% de concentration dans l'atmosphère, la catalase fut réduite de 50% environ en 48 heures. L'azote n'a pas un effet semblable.

ZUSAMMENFASSUNG

Die Katalase-Aktivität war variabel bei den unter Stanstard-Bedingungen untersuchten 3 Spezies und zwei Varianten von Mycobakterien.

Die Katalase-Aktivität erwies sich als eine spezielle Eigenschaft jeder untersuchten Spezies oder Variante von Mycobakterien.

Die Katalase-Aktivität der untersuchten Spezies stand nicht in direktem Verhältnis zu ihrer Wachstumsgeschwindigkeit.

CO_2 hat eine hemmende Wirkung auf die Katalase-Aktivität; bei einer Konzentration von 100% in der Atmosphäre verringerte sich die Katalase-Aktivität innerhalb von 48 Stunden um ungefähr 50%. Stickstoff hat keine solche Wirkung.

REFERENCES

1 Hahn, M.: "Immunisierungs-und Heilversuche Mit den Plasmatischen Zellsäften von Bacterien," *Münch. med. Wschr.* 48:1344, 1897.

2 Middlebrook, G.: "Isoniazid-resistance and Catalase-activity of Tubercle Bacilli," *Am. Rev. Tub.* 69:471, 1954.

3 Neumayr, R. B.; Morse, P. Z., and Morse, W. C.: "Relationship Between Isoniazid Resistance, Endogenous Catalase Activity and Guinea Pig Pathogenicity of Mycobacterium Tuberculosis," *Proc. Soc. Exp. Biol. Med.* 89:468, 1955.

4 Meissner, G., and Bönicke, R.: "Die Beziehungen zwischen Katalase-Inaktivierung, Sensibilitätsminderung für Isoniazid und Virulenzschädigung für das Meerschweinchen," *Beitr. Klin. Tub.* 116:501, 1957.

5 Peizer, L. R., and Widelock, D.: "A Calorimetric Test for Measuring Catalase Activity of Cultures of M. tuberculosis," *Am. Rev. Tub.* 21:305, 1955.

6 Wolinsky, E.; Smith, M. M., and Steenken, W.: "Isoniazid Susceptibility, Catalase Activity, and Guinea Pig Virulence of Recently Isolated Cultures of Tubercle Bacilli," *Am. Rev. Tub.* 73:768, 1956.

7 Stief, M., and Hall, W. H.: "Acid-fast Bacilli not Pathogenic for Guinea Pigs," *Am. Rev., Tub.* 74:478, 1956.

8 Takahashi, Y.; Kuze, A.; Arima, J., and Yamamoto, K.: *Chem. Abstr.* 51:12208f, 1957.

9 Besta, B.; Lucchesi, M., and Malaguzzi, F.: "Sull'attivitá Catalasica del Mycobacterium Tuberculosis," *Ann. Ist. Forlanini* 16:41, 1956.

10 Fujita, A., and Kodama, T.: "Manometrische Bestimmung der Katalase," *Biochem. Z.* 20:232, 1931.

11 Finlayson, M. K., and Edson, N. L.: "The Catalase Activity of Mycobacteria," *Trans. Royal Soc. New Zealand* 77:284, 1947.

12 Darzins, E.: *The Bacteriology of Tuberculosis,* Univ. Minnesota Press, 1958.

Fibroepithelial Polyps of the Bronchus:

A Case Report and Review of the Literature

DAVID T. ROWLANDS, JR., M.D.*
Cincinnati, Ohio

Benign tumors of the bronchi are rare. Unless recognized and treated they may result in severe, even fatal pulmonary damage or unnecessarily radical surgery. The purpose of this case report is to describe such a lesion in a 38 year old man, to illustrate its pathologic anatomy, and to discuss its etiology.

A 38 year old policeman experienced a sharp right anterior chest pain 10 days prior to admission on July 12, 1957. The pain was aggravated by deep breathing and coughing and was accompanied by mild fever. Cough, productive of white-yellow to red streaked sputum, began eight days before admission and there was shortness of breath with progressive intensity.

Five years earlier he had sustained fractures of the right seventh to eleventh ribs and left ninth rib in an automobile accident. He recovered without incident. However, during succeeding years "pneumonia" developed in the right lung on an average of twice each winter. Each episode lasted approximately two weeks and responded promptly to penicillin and Terramycin therapy. He was bothered by a chronic nonproductive cough. Until one year prior to admission he smoked three packs of cigarettes a day but thereafter smoking was limited to an occasional cigar. As an infant he had had two attacks of whooping cough.

Physical examination disclosed a well developed and well nourished white man. The blood pressure was 105/65 mm. Hg: pulse 76/ min; respirations 28/ min; and temperature 99.6° F. The chest expanded symmetrically and both diaphragms moved. Over the base of the right lung there was a decrease in resonance, vocal fremitus, and breath sounds. A few coarse rales were audible. The heart was normal; cyanosis, pallor, clubbing and edema were absent. The physical examination was otherwise not remarkable.

Laboratory Studies: The white blood cell count ranged between 10,500 and 21,100 (admission). There were 85 per cent neutrophils; hemoglobin 13.4 gram/100 cc.; hematocrit 43 per cent. The urine was negative. A precipitin test for syphilis was negative. Sputum smears and culture were negative for tubercle bacilli on six exami-

*Formerly at Veterans Administration Hospital. Now at Cincinnati General Hospital, Department of Pathology.

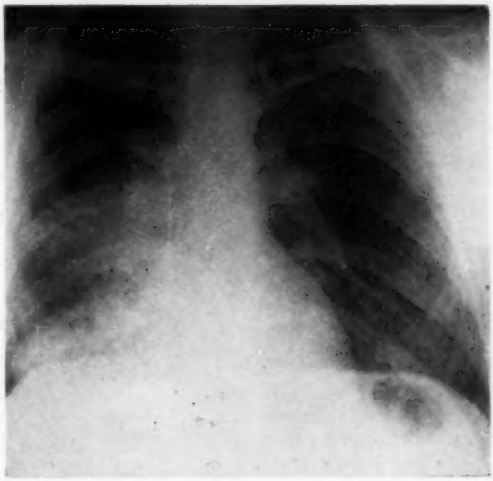


FIGURE 1. The admission x-ray shows a pneumonic infiltrate involving the right middle lobe and the superior segment of the right lower lobe.

nations and fungi were not seen in four specimens. Bacteriologic culture of the sputum yielded a mixture of organisms which included staphylococcus aureus hemolyticus. Subsequent sputum cultures were negative.

A chest roentgenogram on admission demonstrated an infiltrate in the right middle lobe and the superior segment of the right lower lobe (Figure 1). Progressive but incomplete clearing of the pneumonia ensued.

Administration of penicillin was discontinued after seven days because of rapid improvement of symptoms. Bronchoscopy one month after admission to the hospital disclosed the larynx and trachea to be normal. An annular multinodular white mass was noted 1 cm. below the level of the right upper lobe bronchial orifice. A biopsy specimen consisted of four gray-white fragments of tissue measuring as much as 2 mm. in the greatest dimension. Microscopic examination revealed a fibrovascular stroma containing a moderately severe lymphocytic inflammatory infiltrate. Normal bronchial glands were embedded in the stroma which was covered by mucosa varying from a respiratory to a stratified squamous epithelium. There was no evidence of neoplasm.

After a week, bronchoscopy was repeated and the previous observations were confirmed. Another biopsy specimen consisted of three fragments of gray-white soft tissue measuring as much as 5 mm. in diameter. The stroma was similar to that seen in the initial biopsy. The surface epithelium, however, was composed uniformly of stratified squamous epithelium.

A week after bronchoscopy the middle and lower lobes of the right lung were resected. Postoperatively mild temperature elevation was noted during the first few days. On the fifth postoperative day much mucoid secretion was aspirated through a bronchoscope. At the time of bronchoscopy the right upper lobe bronchus was patent and the amputation stump was hyperemic but it was otherwise normal. Thereafter the patient's progress was satisfactory. He was discharged one month after the pulmonary resection. He was examined two months after discharge at which time he was asymptomatic.

The surgical specimen (Figure 2) consisted of the middle and lower lobes of the somewhat firmer than usual right lung. In the proximal bronchial segment there

FIGURE 2. The gross surgical specimen shows polypoid tumors at the line of resection and within the bronchus.

were two groups of pedunculated pearly white tumors, the largest measuring 9 x 6 x 3 mm. Similar lesions were present in the anterior basal segment bronchus 1 cm. distal to its origin. The tumors emerged on broad based pedicles from the bronchial lining and appeared covered by intact mucosa. They caused partial occlusion of the lumen.

Microscopically the mucosal surface was covered by normal bronchial respiratory epithelium focally replaced by nonkeratinizing stratified squamous elements. The core of the polyps consisted of a dense fibrovascular stroma containing a scattered lymphocytic exudate. At the base of one polyp a few groups of residual bronchial glands were manifest. None of these were of neoplastic nature. Pulmonary alveoli were partially collapsed but contained no exudate. In sections of the middle lobe there were foci of organizing chronic pneumonia. The pleura was thickened and fibrotic. No inclusion bodies were recognized.

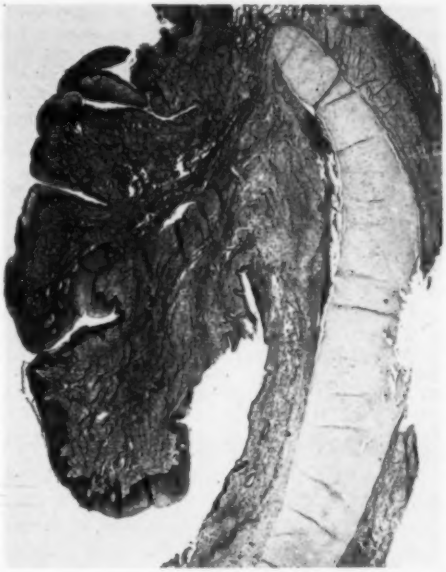


FIGURE 3. A photomicrograph of a single tumor shows the squamous metaplasia which in large part replaces the normal surface epithelium. The fibrovascular nature of the stroma as well as the dearth of inflammation is well demonstrated.

Discussion

Polypoid overgrowths of bronchi are uncommon. In 1938, Pollak, Cohen, and Gnasi[4] in a summary of the literature pertaining to benign bronchial tumors cited 27 cases recognized at autopsy and 77 encountered during life. A review of these disclosed that one necropsy case was a simple polyp and fibroepithelial polyps were observed in 11 living patients. The youngest of the 12 patients was 6 years and the oldest 63 years. The greatest proportion of patients were in the fourth and fifth decades of life. In this paper the case of a 55 year old man, thought clinically to have bronchial carcinoma was reported. Autopsy revealed an inflamed polyp obstructing the right upper lobe bronchus.

In 1940, Samson[6] referred to a 34 year old male with a polypoid lesion of the bronchus associated with chronic purulent inflammation of the bronchus. The stroma of this polyp was highly vascular and exhibited early fibrosis. Regression of the lesion apparently occurred with improvement of the pulmonary infection. Ashmore[1] in 1954 reported a tumor at the junction of the lateral and anterior basal divisions of the lower lobe bronchus in a 51 year old white woman. The mucosa was heaped up into frond-like projections and microscopically exhibited fibrovascular stroma covered by respiratory type epithelium. Schaff and Thomson[7] in 1955 reported recurrent multiple small bronchial polyps with fibrovascular stroma in a 57 year old man who was followed for 17 years with frequent bronchoscopic examinations. In 1957 Rodo[5] reported an additional case in a 40 year old man who remained well 1½ years after adequate surgical therapy.

Inflammatory polyps should be distinguished from true papillomas of the respiratory tract which are characterized by papillary proliferation of the stratified squamous epithelium. Ullman[8] has presented strong evidence for a viral etiology of papillomas of this type occurring in the larynx. However, no such evidence exists in relation to bronchial polyps. Jackson[2] has emphasized the role of inflammation in their pathogenesis. Peroni[3] was unable to produce bronchial polyps in dogs by trauma, experimental infection, or chemical irritation. He concluded that bronchiectasis and endobronchial suppuration were complications of bronchial tumors rather than causative factors.

Inflammatory polyps are readily distinguished from other polypoid bronchial tumors by miscroscopic examination. They exhibit neither the squamous epithelial overgrowth of papillomas nor the bizarre and varied patterns of bronchial adenomas and carcinoma. Highlighting the lesion is a polypoid overgrowth of fibrovascular stroma infiltrated by a variable number of inflammatory cells. These are frequently lymphocytes. The overlying mucosal epithelium retains its normal respiratory character but squamous metaplasia is not infrequent. The etiology is unknown. When confined to bronchi these lesions appear to occur most often in middle age. Pneumonia is a frequent complication and usually calls attention to the presence of the lesion.

Despite the temporal relation of the onset of respiratory symptoms in the present case to the severe chest injury sustained five years before operation, this instance may represent simply a coincidental occurrence.

REFERENCES

1 Ashmore, P. G.: "Papilloma of the Bronchus," *J.Thoracic Surgery*. 27: 293, 1954.

2 Jackson, C., and Jackson, C. L.: "Benign Tumors of the Trachea and Bronchi," *J.A.M.A*. 99: 1747, 1932.

3 Peroni, A.: "Inflammatory Tumors of the Bronchi," *Arch. Otolaryngology*. 19: 1, 1934.

4 Pollak, B. S., Cohen, S., Gnassi, A. M.: "Inflammatory Bronchial Tumors," *Archives of Otolaryngology*. 27: 426, 1938.

5 Rodo, J. E.: "Fibroma De Bronquio," *Medicina*. 17: 247, 1957.

6 Samson, P. C.: "Diffuse Polypoid Laryngotracheobronchitis," *Journal of Thoracic Surgery*. 9: 679, 1940.

7 Schaff, B., and Thomson, R. V.: "Papillomatosis of the Trachea and Bronchi," *Am. Review of Tuberculosis*. 71: 429, 1955.

8 Ullmann, E. V.: "On the Aetiology of the Laryngeal Papilloma," *ACTA Oto-laryngologia*. 5: 317, 1923.

SECTION ON CARDIOVASCULAR DISEASES

The Effects of Smoking on the Peripheral Circulation*

GRACE M. ROTH, Ph.D.** and RICHARD M. SHICK, M.D.†
Rochester, Minnesota

We have been particularly interested in the problem of smoking on the peripheral vascular system of man. Because a man in good health may feel that smoking is bad only for one who is ill, information concerning the effect of smoking on normal individuals is important. Therefore, a total of 425 smoking tests was carried out on normal individuals. Because we wished to know also the effect of smoking tobacco on patients with peripheral vascular disease, further studies were carried out on such patients.

A standard smoking test has been devised. We expected little difficulty in determining the effect of smoking tobacco on the circulation of normal individuals. However, all methods of measuring peripheral blood flow in man are indirect, and certain factors that affect peripheral blood flow must be considered in order to obtain comparable measurements. Some of the confusion in the results of smoking tests has arisen because too little attention has been paid to (1) the environmental temperature,[1] (2) the position of the subject, particularly of the extremities, (3) the taking of food, and (4) the basal metabolic rate.

The standard smoking test, as finally devised, used the skin temperatures as a measurement of blood flow. It took into consideration the four factors just listed and also required simultaneous observations of blood pressures, pulse rates and skin temperatures. The smokers inhaled with their accustomed depth and frequency during the 12 to 15 minutes required to smoke two thirds of two commercially available cigarettes.

The Normal Person

In an early study an attempt was made to determine how consistent were the results of the use of tobacco, whether a tolerance to smoking develops in habitual smokers and whether nicotine is the substance in smoke that causes the vascular effect. Sixty-six standard smoking tests were carried out on six normal subjects who were habitual smokers, four physicians and two women technicians whose basal metabolic rates ranged from −13 to +10 per cent. These studies showed that the responses to smoking of the skin temperature of the same individual varied from day to day according to the basal metabolic rate, but the increase of the blood pressure and pulse rate during smoking varied

*Presented at the 24th Annual Meeting, American College of Chest Physicians, San Francisco, California, June 18 to 22, 1958.
**Section of Physiology, Mayo Clinic and Foundation. Presently at Albuquerque, New Mexico.
†Section of Medicine, Mayo Clinic and Mayo Foundation.

little from day to day. Thus, it became evident that the basal metabolic rate should be determined in each study with skin temperatures.

The skin temperature of the toes of all the subjects decreased an average of 2.5° C. (4.5° F.) with a range from 1° to 4° C. (1.8° to 7.2° F.) during smoking. For the fingers the average decrease was 3.2° C. (5.8° F.). The average increase of blood pressure during smoking was 20 mm. of mercury systolic and 14 mm. diastolic. The pulse rate increased an average of 36 beats per minute; the range was from 20 to 52 beats. The electrocardiographic changes consisted of increased heart rate, decreased amplitude of T waves and inverted T waves in one instance.

Habitual smokers did not show tolerance to the effects of smoking as the skin temperatures of the extremities decreased and the blood pressure and pulse rate increased. The decrease of the skin temperature was not related to the length of time the subject had been a smoker or the number of cigarettes smoked a day.

Several groups of additional tests were necessary to determine whether the vascular changes were due to nicotine and how much the content of nicotine had to be decreased to banish the vascular effects. Normal subjects were given a solution of sodium chloride intravenously as a control, and then 2 mg. of nicotine was added to the solution without the subjects' knowing when it was added. The skin temperatures of these persons decreased rapidly and definitely, the heart rate increased,

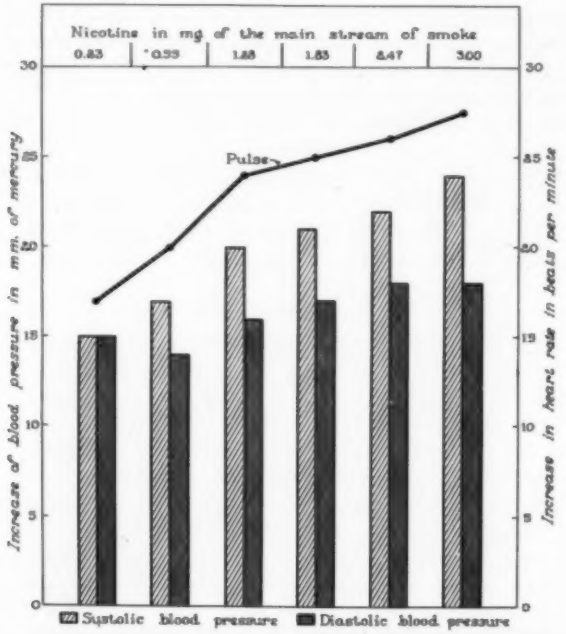


FIGURE 1: The effect on the blood pressure and pulse rate caused by smoking two cigarettes, the main stream of the smoke of which contained various concentrations of nicotine. The pulse and blood pressure increased sharply when the concentration of nicotine increased from 0.55 mg. to 1.28 mg.

and the amplitude of the T waves in the electrocardiographic tracing decreased with administration of nicotine.

The second group of tests consisted of 30 smoking tests with various commercially available denicotinized cigarettes. The vascular effects were similar to those obtained when standard cigarettes were smoked.

To determine how much the content of nicotine in a cigarette should be decreased to banish the vascular effects of smoking, 192 standard smoking tests were done on 29 normal subjects who were between 20 and 36 years of age. Six different batches of cigarettes were used. The main stream of smoke from one cigarette of each batch contained respectively an average of 0.23, 0.55, 1.28, 1.83, 2.47 and 3 mg. of nicotine. As the concentration of nicotine in the main stream of the smoke was increased, the skin temperatures of both the fingers and toes decreased until the effects were the same as those from standard cigarettes (Fig. 1). The lower the concentration of nicotine in the smoke the less the blood pressure and pulse rate increased (Fig. 2) from the basal level and vice versa. The increase was sharp when the concentration of nicotine was raised from 0.55 to 1.28 mg. This study indicated that nicotine is responsible for the vascular changes which accompany smoking, and these observations explain why the same vascular effects were obtained during the smoking of standard cigarettes and denicotinized cigarettes. Apparently, the content of nicotine in a cigarette must be decreased more

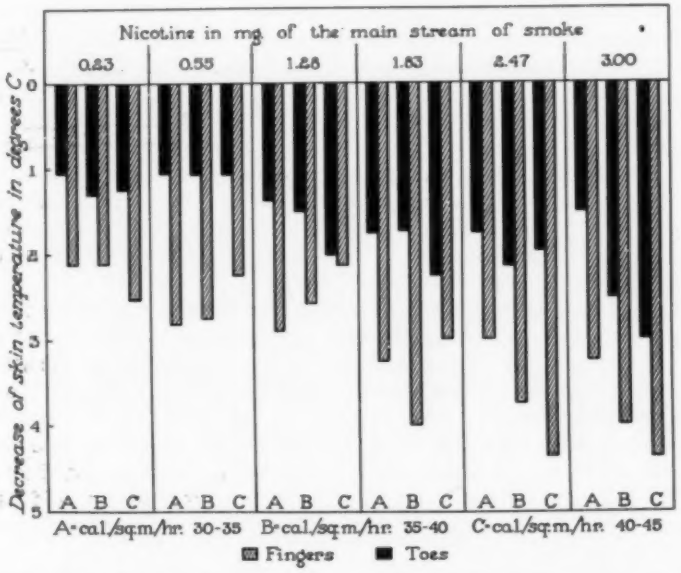


FIGURE 2: Effect on the skin temperature of the toes and fingers caused by smoking two cigarettes, the main stream of the smoke of which contained various concentrations of nicotine. Observations of the effects of each concentration of nicotine were divided into three groups, A, B and C, according to the basal heat production. As compared with the fingers, the decrease in skin temperature of the toes was less, particularly in groups A and B, irrespective of the concentration of nicotine. Also, as the concentration of nicotine was increased, the decrease of the skin temperatures became greater.

than 60 per cent from that in a standard cigarette before smoking produces only slight or no vascular effects.

The normal person often feels that alcohol will inhibit the vascular effects of smoking since the oral administration of alcohol dilates the blood vessels of the extremities. To study this problem we carried out smoking tests in the usual way and on the next day we investigated the effect of smoking after the taking of alcohol on the same persons. To do this we carried out 87 smoking tests after the ingestion of 1 ounce of 95 per cent alcohol in fruit juice. Smoking began between 30 and 60 minutes after the ingestion of the alcohol at the height of the vasodilation as measured by the increase in the skin temperature. The blood pressure and pulse rate rose definitely on smoking after the ingestion of alcohol. The skin temperature of the fingers and toes decreased below the basal level on smoking after ingestion of alcohol in 72 per cent of the subjects. Alcohol in this study did not prevent vasoconstriction from smoking.

In the normal person, then, tolerance does not develop to tobacco so far as the vascular effects are concerned; the blood pressure and pulse rate increase and the skin temperature of the extremities decreases on smoking tobacco; nicotine appears to be the most important factor in producing the vascular effects, and alcohol does not nullify the effect of smoking.

Effect in Peripheral Vascular Disease

The effects of smoking on patients with peripheral vascular disease as determined by the smoking test are a significant fall in the skin temperatures of the fingers and toes and a rise in blood pressure and pulse rate. The variations are similar to those of normal subjects and most likely are in association with the basal metabolic rate.

The evidence that smoking plays a role in the progression of peripheral vascular disease is no longer controversial.[2] Although it may not be the etiologic factor, it is certainly the most prominent contributing factor. A nonsmoker rarely, if ever, is seen with thromboangiitis obliterans at the Mayo Clinic, and various reports have been made of the relief of symptoms after cessation of smoking.

In view of this, the discussion of filters and filtered cigarettes produced as a protection in removing nicotine and tars from cigarette smoke is highly important. We found that the vascular effects were the same for filtered cigarettes as for nonfiltered cigarettes. The Chemical Laboratory of the American Medical Association[3] has reported that the fraction of nicotine removed from the main stream of the smoke by the filter is small. To avoid the vascular effects, such efficient filters could be made that the culminating achievement would be a filter that would pass no smoke at all. It is exceedingly doubtful that the average smoker would take kindly to this.

Wright[4] did not find any filtered cigarettes that did not produce a response in the vascular system. In addition, he repeatedly observed relapse in thromboangiitis obliterans when patients smoked filtered cigarettes. He described a patient who first had active thromboangiitis obliterans in 1940. On stopping smoking, his symptoms remained quiescent until 1949 when he resumed smoking. In 6 months gangrene of

three toes developed. Once more, on abstinence from smoking the disease became quiescent. Four months after beginning to smoke filtered cigarettes, his disease has been reactivated, and he has early pregangrenous involvement of two toes.

Mediation of the Vasoconstriction Due to Smoking

Earlier workers attributed the vasoconstriction of the peripheral blood vessels by smoking to stimulation of the sympathetic nervous system and questioned whether the absorbed nicotine caused the whole effect. Rapaport, Frank and Massell[5] reported that lumbar sympathectomy abolished the peripheral vasoconstriction produced by smoking in the lower extremities of 19 patients. They concluded that the vasoconstriction, therefore, is mediated by sympathetic vasomotor fibers and not by humoral agents such as epinephrine or posterior pituitary hormone. We also have found (Fig. 3) no vasoconstriction as indicated by a decrease in the skin temperature of the toes during smoking if lumbar sympathectomy was complete, but smoking decreased the skin temperatures of the fingers. Thus after lumbar sympathectomy the intact sympathetic nervous system seems to function in a more than adequate manner.

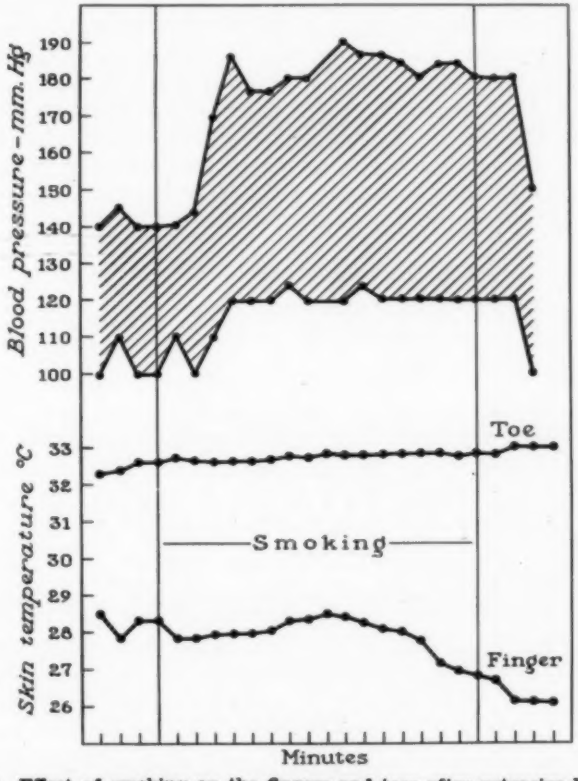


FIGURE 3: Effect of smoking on the fingers and toes after extensive lumbar sympathectomy. Reversal of temperatures of the fingers and toes, with no effect of smoking on the temperatures of the toes but a mild fall on temperatures of the fingers, should be noted.

Schmiterlow[6] in 1948 showed that norepinephrine is present in the wall of the peripheral arteries. Haimovici[7] reported from profusion experiments in animals that nicotine may act directly on the blood vessels because the vasoconstrictor action of nicotine occurred even after the removal of the sympathetic chains and of the spinal nerves. According to Burn and Rand[8] this vasoconstriction in the rabbit is due to the release of norepinephrine from the wall of the arteries. Several workers have presented evidence for and against the theory that smoking increases the secretion of epinephrine and norepinephrine with a subsequent elevation in the blood sugar.

With newer methods available, Rehder and one of us (Roth[9]) attempted to determine whether smoking of tobacco increased the production of epinephrine and norepinephrine in man and in turn increased the blood sugar. We carried out smoking tests on 24 normal subjects under basal conditions. During the control period blood was drawn through a siliconized needle for blood sugars determined by the Somogyi[10] and Nelson[11] method and epinephrinelike substances determined by the method of Weil-Malherbe and Bone.[12] Skin temperatures, blood pressure and pulse rates were measured at 10-minute intervals. Blood was drawn for determination of blood sugar at intervals of 3, 5, 10 and 15 minutes after smoking was begun and for pressor amines between 3 and 5 minutes after smoking was begun. We measured the skin temperature, blood pressure and pulse rate at 1-minute intervals during smoking. The levels of the fasting blood sugar and the epinephrinelike substances of the systemic blood did not rise appreciably. However, a definite stimulation of the sympathetic nervous system occurred as evidenced by the significant rise of the pulse rate and blood pressure and the decrease of the skin temperatures of the fingers and toes.

SUMMARY

Because a man in good health may feel that smoking is bad only for one who is ill, information concerning the effect of smoking on normal individuals is important. Therefore, a total of 425 smoking tests was carried out on 100 normal individuals.

The standard smoking test, as finally devised, used the skin temperatures as a measurement of blood flow together with measurements of blood pressure and pulse rate.

Our studies disclosed that on the normal person tolerance does not develop to tobacco so far as the vascular effects are concerned; the blood pressure and pulse rate increase and the skin temperature of the extremities decreases on smoking tobacco; nicotine appears to be the most important factor in producing the vascular effects, and alcohol does not nullify the effect of smoking.

The effects of smoking on patients with peripheral vascular disease as determined by the smoking test are similar to those of normal subjects and most likely are in association with the basal metabolic rate.

The evidence that smoking plays a role in the progression of peripheral vascular disease is no longer controversial.

We found no vasoconstriction as indicated by a decrease in the skin temperature of the toes during smoking when lumbar sympathectomy was complete, but smoking decreased the skin temperatures of the fingers.

Rehder and Roth found also that the levels of the fasting blood sugar and the epinephrinelike substances of the systemic blood did not rise appreciably with smoking.

RESUMEN

Puesto que un hombre en buen estado de salud puede creer que el fumar sólo es dañoso para los enfermos, es importante el estudio de los efectos del fumar en los sujetos normales.

Por tanto, se hicieron 425 pruebas de fumar en individuos normales y más estudios se hicieron en enfermos con enfermedad vascular periférica.

La prueba estandar del fumar como finalmente se ideó, fué la medida de las temperaturas cutáneas como reveladora del flujo sanguíneo.

Nuestros estudios descubrieron que en las personas normales no desarrollan tolerancia al tabaco en lo que se refiera a los efectos vasculares; la presion sanguínea y la frecuencia del pulmón aumentan y la temperatura cutánea de las extremidades, decrece al fumar tabaco; la nicotina parece ser el factor más importante para producir los efectos vasculares y el alcohol no nuiifica los efectos del tabaco.

Los efectos del fumar en los enfermos vasculares periféricos según se ha determinado por estas pruebas, son similares a los que se observan en los sujetos normales y muy probablemente se asocian con los cambios del metabolismo basal.

Ya no se presta a controversia la evidencia que el fumar desempeña un papel en la evolucion de la enfermedad vascular periférica.

No encontramos vasoconstricción según lo indica el decrecimiento de la temperatura de la piel en los dedos gordos del pie durante el fumar cuando la simpatectomía lumbar era completa, pero el fumar hacía decrecer la temperatura de los dedos de la mano.

Rehder and Roth también encontraron que los niveles de la glucemia en ayunas y las substancias similares a la epinefrina en la sangre de la circulación mayor no subieron notablemente al fumar.

RESUMÉ

Parce qu'un homme en bonne santó peut penser que fumer n'est mauvais que pour celui qui est malade, il est important de donner des renseignements sul l'effet de la fumée sur des individus normaux. C'est pourquoi les auteurs ont pratiqué 425 tests à la fumée chez des individus normaux, et des études ultérieures furent pratiquées sur des malades atteints d'affections vasculaires périphériques.

Le test standard à la fumée, selon sa dernière mise au point, utilisa les températures cutanées comme mesure du débit sanguin.

Nos études révélèrent que chez l'individu normal, l'intolérance au tabac ne se développe pas tant que les effets vasculaires ne sont pas perceptibles; la pression sanguine et le pouls augmentent et la température cutanée des extrémités décroit à l'occasion de la fumée; la nicotine semple être le facteur le plus important dans la production des effets vasculaires, et l'alcool n'annule pas l'effet de la fumée.

Les effets de la fumée sur les malades atteints d'affection vasculaire périphérique, selon ce qui a été determiné par le test, sont semblables à ceux produits chez les sujets normaux et sont plus vraisemblablement en association avec le taux du métabolisme basal.

L'évidence selon laquelle la fumée joue un rôle dans la progression de l'affection vasculaire périphérique n'est plus controversée.

Nous n'avons pas trouvé de vasoconstriction qu'aurait indiqué la diminution de la température cutanée des orteils pendant que l'individu fume lorsqu'il avait subi une sympathectomie lombaire complète, mais la fumée fit décroitre les températures cutanées des doigts.

REHDER et ROTH trouvèrent également que le taux du sucre sanguin et des substances de la circulation générale voisines de l'adrénaline ne s'élevait pas considérablement avec la fumée.

ZUSAMMENFASSUNG

Da ein Mann, der bei guter Gesundheit ist, glauben könnte, dass Rauchen nur schädlich ist für jemanden, der krank ist, sind Informationen über die Wirkung des Rauchens bei normalen Personen von Wichtigkeit. Es wurden daher insgesamt 425 Rauch-Teste bei normalen Versuchspersonen durchgeführt, und weitere Untersuchungen angestellten bei Kranken mit peripheren Gefässerkrankungen.

Der Standard-Rauchtest, wie er schliesslich ausgedacht wurde, machte Gerbrauch von der Hauttemperatur als Mass der Durchblutung. Unsere Untersuchungen erwiesen, dass sich bei normalen Personen so weit keine Tabak-Verträglichkeit entwickelt, wie es die Gefässwirkungen angeht; Blutdruck und Pulsfrequenz nehmen zu, und die Hauttemperatur der Extremitäten nimmt beim Rauchen von Tabak ab; Nikotin scheint der wichtigste Faktor zu sein für das Zustandekommen der Gefässdefekte, und der Alkohol hebt die Wirkung des Rauchens durchaus nicht auf.

Die Wirkungen des Rauchens auf Patienten mit peripheren Gefässerkrankungen gemäss deren Bestimmung durch den Rauchtest sind ähnlich denen normaler Versuchspersonen und stehen sehr wahrscheinlich in Verbindung mit dem Grundumsatz.

Das Beweismaterial, wonach das Rauchen eine Rolle spielt für die Progredienz peripherer Gefässerkrankung, ist nicht länger umstritten.

Wir fanden keine Vasokonstriktion, wie sie bemerkbar wird an einer Abnahme der Hauttemperatur der Zehen während des Rauchens, wenn eine komplette, lumbale Sympathektomie vorlag; aber das Rauchen setzte die Hauttemperatur der Finger herab.

Rehder und Roth fanden ausserdem, dass der Nüchtern-Blutzucker-Spiegel und derjenige von epinephrinartigen Substanzen im grossen Kreislauf beim Rauchen nicht messbar anstieg.

REFERENCES

1 Roth, Grace M.: "Tobacco and the Cardiovascular System: The Effects of Smoking and of Nicotine on Normal Persons," Charles C. Thomas, Springfield, Illinois, 1951, 66 pp.

2 Gifford, R. W. and Hines, E. A.: "Complete Clinical Remission in Thromboangiitis Obliterans During Abstinence From Tobacco: Report of Case," *Proc. Staff Meet., Mayo Clin.*, 26:241, 1951.

3 Chemical Laboratory: "A Study of Cigarettes, Cigarette Smoke, and Filters," *J.A.M.A.*, 157:1309, 1955.

4 Wright, I. S.: "Cigarettes," *J.A.M.A.*, 155:666, 1954.

5 Rapaport, S. I.; Frank, H. A., and Massell, T. B.: "The Effect of Smoking Upon Blood Flow in the Sympathectomized Limb," *Circulation*, 2:850, 1950.

6 Schmiterlöw, C. G.: "The Nature and Occurrence of Pressor and Depressor Substances in Extracts from Blood Vessels," *Acta physiol. scandinav.*, Suppl. 56, pp. 1-113, 1948.

7 Haimovici, Henry: "Postganglionic Site of Action of Nicotine With Special Reference to Its Direct Action on Blood Vessels," *Proc. Soc. Exper. Biol. & Med.*, 68:516, 1948.

8 Burn, J. H. and Rand, M. J.: "Noradrenaline in Artery Walls and Its Dispersal by Reserpine," *Brit. M. J.*, 1:903, 1958.

9 Rehder, Kai and Roth, Grace M.: "The Effect of Smoking on the Fasting Blood Sugar and Pressor Amines," (Unpublished data).

10 Somogyi, Michael: "A New Reagent for the Determination of Sugars," *J. Biol. Chem.*, 160:61, 1945.

11 Nelson, Norton: "A Photometric Adaptation of the Somogyi Method for the Determination of Glucose," *J. Biol. Chem.*, 153:375, 1944.

12 Weil-Malherbe, H. and Bone, A. D.: "The Adrenergic Amines of Human Blood," *Lancet*, 1:974, 1953.

Beta Hemolytic Streptococci and Rheumatic Fever in Miami, Florida

II. Antistreptolysin O Titer Determinations between October 1954 and May 1955

MURRAY M. STREITFELD, Ph.D., and MILTON S. SASLAW, M.D., F.C.C.P.*
Miami, Florida

The host response to beta hemolytic streptococci can be evaluated best if clinical, bacteriological and immunological data are available.[1] Host status is important because the incidence of group A beta hemolytic streptococcal infections has been related, statistically, to the occurrence rate of acute rheumatic fever, in that this disease has been reported to follow 3 per cent of streptococcal infections.[2] The present report considers the assistance in determining host status that may be derived from one immunologic test, the antistreptolysin-O (ASLO) serum titer.

In our own investigations in Greater Miami (Dade County), Florida, we recovered group A beta hemolytic streptococci commonly;[3-6] over 40 per cent of school children, eight to nine years of age were found to harbor group A organisms in their throats at least once per eight-month school year, when cultures were taken monthly; an average monthly recovery rate of approximately 15 per cent applied to the same age group.[7] However, acute rheumatic fever and rheumatic heart disease have been observed to occur rarely,[5,6,9] in far less than 3 per cent of the children harboring group A streptococci.

The concept that approximately 3 per cent of all streptococcal infections are followed by definite rheumatic fever episodes, appears to be based on data representing clinical illness due to streptococci.[2,10] Clinical illness, however, need not be present, for "approximately 40 per cent of infections produce few if any symptoms, so that many infections caused by these organisms go unrecognized."[10] Because of our finding of infrequent acute rheumatic fever episodes despite the ubiquitous presence of streptococci, we considered that a study of the qualitative and quantitative serologic response of the host to these organisms might assist in explaining the discrepancy between the streptococcal-rheumatic statistical relationship reported elsewhere and our own observations.

Methods and Materials

Blood was drawn from the anterior cubital vein of each of 333 children, six to nine years of age, attending three public schools of Dade County, Florida; the schools were selected to represent white and negro races, of low and medium incomes.[5,6] These blood samples were obtained in October 1954, at the same time that initial swabbings were taken from the throats of the same children for bacteriologic study.[5,6] Routinely, throat cultures were collected monthly from the same children. When-

*Department of Medical Research, National Children's Cardiac Hospital, Department of Bacteriology, University of Miami, School of Medicine, and the Department of Microbiology, University of Miami. Supported in part by funds from the Florida State Board of Health and grant H-1738, Public Health Service.

ever a beta hemolytic streptococcus was isolated from the throat of a child, subsequent throat swabbings and blood drawings were carried out 2, 4, 8, 16 and 32 weeks later, until the studies terminated in May 1955. In May, blood was drawn again on each of the 286 children remaining in the study. Forty-seven of the original 333 children who participated in the program did not complete the project; 27 were transferred to schools other than those three in which the investigations took place; 20 children were dropped at parents' requests. In 50 of the remaining 286 children, blood samples were not studied, because of parental refusals to permit serial blood drawing, or, in a few instances, because of hemolysis or other technical difficulties.

Each sample of blood was collected in a B-D silicone-coated Vacutainer*. We found this collection method easier than with syringe, and it gave us few hemolyzed samples. All blood specimens were allowed to clot, and were centrifuged. The supernatant sera were drawn off, placed in sterile screw-capped vials, and stored in the deep-freeze until June 1955, when antistreptolysin O titrations were carried out, according to previously described technique,[11] using commercial streptolysin-O (Difco).

Calculations: — Average ASLO titers were calculated according to age, sex, race, and streptococcal findings. Average indices were determined also because they provide an effective simple technique for evaluating large series of data of this type.[12] Calculations were accomplished as previously described,[4,12] utilizing arbitary arithmetic ranks to represent each titer level assayed (e.g. 1 = titer < 12; 2 = titer 12; . . . . . ; 13 = 2500); the titer ranks of all sera studied then were averaged to give the index.

The use of arithmetic ranks introduced minor mathematical errors in evaluation of ASLO responses, since arithmetic ranks are not exactly proportional to titer values. Titer values, based on antilogs of particular serum dilutions, showed that close agreement between arithmetic ranks and logarithmic values occurred if the following modified ranks were employed: < 12 = 1; 12 = 3; 50 = 8; 100 = 10; 125 = 11; 166 = 12; 250 = 13; 333 = 14; 500 = 15; 625 = 16; 833 = 17; 1250 = 18; and 2500 = 20. (A titer value of 6 was used to represent the titer of sera with values of < 12.) In the present report, ASLO indices were calculated on both arithmetic and modified bases.

Results

Initial and final ASLO titers were available from 236 children. The average titers and indices for boys (av. titer, 103.5; arithmetic index, 3.95; modified index, 7.96) and girls (101.3, 3.96, 8.15) were approximately the same. When the data are considered from the standpoint of grade, children in the third year of school (ages 8-9) showed lower average ASLO titer and indices (90.7, 3.64, 7.59) than those children in either of the other two grades (1st grade = 99.9, 3.93, 7.96; 2nd grade = 119.2, 4.35, 8.79).

White children had more titers of 250 units and above (10.2 per cent) cent) than had negroes (7.1 per cent); they also had more low titers,

*Kindly contributed by the Becton-Dickinson Co., Rutherford, New Jersey.

of < 12 units (16.9 per cent among white children; 1.2 per cent among negroes) and of 12 units (25.5 per cent in whites; 13.5 per cent in negroes). ASLO titers of < 12 were obtained from 30 of the 236 children (12.3 per cent) in October 1954, and from 23 children (9.7 per cent) in May 1955. Nineteen children had low titers on both occasions. The average titers for each of the two white schools (106.3 and 96.0) and the negro school (103.4) were approximately the same. Nevertheless, both arithmetic and modified ASLO indices were higher in the negro school (4.24, 9.24) than in either of the two white schools (3.83, 7.48; 3.75, 7.35).

The lowest average initial and final antistreptolysin O titers and indices were observed in the sera of those children from whose throats no beta hemolytic streptococci (69.4, 3.2, 6.40) or from the sera of those two children from whom only group B organisms (12.0, 2.0, 3.00) were isolated. The highest values were obtained in the group A typable category (147.0, 5.1, 10.43), with the group A non-typable category (134.3, 4.7, 9.61) next highest. These results are similar to those observed during the year 1953-1954.[4] Groups C and G streptococci were accompanied by moderate increases in values in both years of study.

Of the 99 children (Table 1) from whose throats no beta hemolytic streptococci were isolated, only five showed a rise in ASLO titer of two tubes or more, when initial and final levels were considered. Group A organisms, typable and non-typable, were accompanied by titer rises in 27.0 per cent and 29.1 per cent respectively.

TABLE 1 — CHILDREN WITH ANTISTREPTOLYSIN O TITER RISES OF 2-TUBES OR GREATER, ACCORDING TO STREPTOCOCCAL ISOLATES, 1954-1955.

Streptococcal Group	Total No. Chiildren	ASLO Response‡	Schools K*	C*	D*	Totals	Per cent Children Showing ASLO Rise
No beta Strep.	99	Rise	2	1	2	5	5.1
		No Rise	43	28	23	94	—
Group A,	37	Rise	8	1	1	10	27.0
typable strains		No Rise	14	4	9	27	—
Group A, non-	55	Rise	4	8	4	16	29.1
typable strains		No Rise	7	9	23	39	—
Group B	2	Rise	0	0	0	0	0.0
		No Rise	0	0	2	2	—
Group C	18	Rise	0	1	2	3	16.7
		No Rise	4	3	8	15	—
Group F	10	Rise	0	0	0	0	0.0
		No Rise	3	2	5	10	—
Group G	8	Rise	0	0	0	0	0.0
		No Rise	2	3	3	8	—
Comb.†	7	Rise	0	0	0	0	0.0
		No Rise	1	3	3	7	—
TOTALS	236	Rise	14	11	9	34	14.4
		No Rise	74	52	76	202	—

*K = Middle income, white school.
C = Low income, white school.
D = Mixed income, negro school.
†Comb. = More than 1 group of beta hemolytic streptococci isolated, excluding group A organisms.
‡Rise = 2 tubes or greater.

TABLE 2 — ANTISTREPTOLYSIN O RESPONSES AS RELATED TO NUMBERS OF COLONIES OF TYPABLE AND NONTYPABLE GROUP A BETA HEMOLYTIC STREPTOCOCCI FOUND ON ORIGINAL ISOLATION PLATES

School	K*			C*			D*			TOTALS				
No. of Colonies#	No. Strains	No† ASLO Rise	ASLO Rise †	No. Strains	No ASLO Rise	ASLO Rise	No. Strains	No ASLO Rise	ASLO Rise	Total Strains	No ASLO Rise No.	Per cent	ASLO Rise No.	Per cent
						I. Typable Strains.								
0-24	15	7	8	9	6	3	14	10	4	38	23	60.5	15	39.5
25-99	2	1	1	0	0	0	0	0	0	2	1	50.0	1	50.0
100 & over	9	1	8	2	2	0	4	2	2	15	5	33.3	10	66.7
Totals	26	9	17	11	8	3	18	12	6	55	29	52.7	26	47.3
						II. Nontypable Strains.								
0-24	19	11	8	14	7	7	33	27	6	66	45	68.2	21	31.8
25-99	0	0	0	3	1	2	2	1	1	5	2	40.0	3	60.0
100 & over	3	1	2	3	0	3	8	6	2	14	7	50.0	7	50.0
Totals	22	12	10	20	8	12	43	34	9	85	54	63.5	31	36.5

*K = Middle income, white school.

C = Low income, white school.

D = Mixed income, negro school.

#No. of Colonies = higher number of colonies on 1 of 2 original plates

† = 2 tube or greater rise.

Data are available to compare antistreptolysin O titers and indices obtained in 1953-1954[4] with those found in 1954-1955 in a group of 66 children followed through both years. The average initial and final titers and indices were uniformly higher the second year of the study than the first. During the first year, the averages were 79.0, 3.58 and 7.61, while corresponding figures for the second year were 120.0, 4.12 and 8.58. During the first year, 23 children's throats yielded group A beta hemolytic streptococci, while 27 were positive during the second year.

Group A streptococcal colony counts were compared with ASLO titer responses (Table 2). Adequate serological data were available for 140 group A streptococcal strains. An ASLO titer rise was considered to be a rise of 2-tubes or greater within one month of isolation of a new group A organism as indicated by a change in type, a change from a non-typable to a typable strain, or the recovery for the first time of a group A streptococcus. Table 2 shows that as colony counts of both typable and non-typable group A strains increased, the likelihood of ASLO rises increased. This relationship was more marked with the typable than with the non-typable organisms. Of the 55 typable strains, 47.3 per cent were accompanied by ASLO rises; 36.5 per cent of the 85 non-typable strains were associated with ASLO rises.

In February and March 1955, an outbreak of group A, type 6 beta hemolytic streptococcus was observed in one school (K) (Table 3). Sera were obtained from 18 children already in our study, according to the routine outlined above for children harboring beta hemolytic streptococci. Seventeen children showed a 2-tube or greater rise in ASLO titer; the remaining child (No. 2085) showed a rise of 1 tube. Titers were observed to rise to levels of 250 to 625 units in 15 instances. Elevated titers began to fall in two to four weeks (1-3 tubes), but did not reach original baselines for any child in this group by the end of the study in mid-May. The absentee rate remained low, and did not appear to be affected by this streptococcal outbreak.

Two hundred thirty-six different incidents* of beta hemolytic streptococcal recovery occurring in 184 children (Table 4)¶ were accompanied by a sufficient number of blood samples closely preceding and following streptococcal isolation to determine whether a rise of 2-tubes or greater in antistreptolysin O titers, or whether no such rise§ had occurred. Typable strains of group A organisms gave the highest percentage of elevations in titer; non-typable strains were next highest, followed in decreasing order by beta hemolytic streptococci of group C, B, G and F. Of the 236 streptococcal incidents, 75 (31.8 per cent) were associated with ASLO titer rises. Titers of 100 and above, when associated with typable or non-typable strains of group A streptococci tended to persist at levels of 100 or higher throughout the eight months of study, whether

*Includes initial isolates of beta hemolytic streptococci, changes in groups, changes in Lancefield type of group A, and change from non-typable group A to typable.

¶Table 4 includes all those streptococcal incidents (236 in 184 children) where serological findings are adequately related in time to permit evaluation of the immunological responses. Previous data[5] listed those children (207) from whose throats no organisms or not more than one Lancefield group were recovered during this year of study.

§Tabulated to include no change in titer, fall in titer, or a rise limited to one tube.

TABLE 3 — ANTISTREPTOLYSIN O RESPONSES AND BACTERIOLOGIC FINDINGS IN CHILDREN HARBORING GROUP A TYPE 6 BETA HEMOLYTIC STREPTOCOCCI DURING "EPIDEMIC" IN SCHOOL K.

Feb. — May, 1955.

Case No.	Oct. 1954	Mid Oct.	Nov.	Mid Nov.	Dec.	Mid Dec.	Jan. 1955	Mid Jan.	Feb.	Mid Feb.	Mar.	Mid Mar.	Apr.	Mid Apr.	May	Mid May
2018	250G	166G	166	125			250G	833G	50G	$500A_6$	$333A_6$	$500A_6$	A_6	$500A_6$	$333A_6$	$333A_6$
2043	$125A_{12}$	125L*	$166A_{12}$	$125A_{12}$	125		100		$100A_{12}$		$125A_{12}$	$125A_6$	$500A_6$	$500A_6$	$333A_6$	$500A_6$
2046	12										A_6					
2054	50								A_6		500					
2055	100										A_6	$625A_6$	$250A_6$	$250A_6$	$166A_6$	A_6
2056	12										A_6		$166A_6$	$166A_6$	$125A_6$	$125A_6$
2057	166										A_6	$333A_0$	250F	166	250	
2058	12								A_6	$250A_6$	$125A_6$	$125A_6$	$125A_6$	$125A_6$	$125A_6$	$100A_6$
2059	125						A_0	A_0	166		A_6	333	$333A_6$	$250A_6$	$250A_6$	250
2061	12										A_6	$166A_6$	250			
2064	12		A_0	A_0	166		A_0	100	$100A_0$	$50A_0$	$50A_6$	$100A_6$	$125A_6$	166	$100A_6$	166
2065	100								A_6	$166A_6$	250		A_6	$166A_6$	$125A_6$	$166A_6$+F
2067	$50A_0$	$50A_0$	A_0	100	50				50		$250A_6$	$625A_6$	$250A_6$	333	A_6	A_6
2077	50						F	<12			A_6	250	$125A_6$	125	$100A_6$	100
2085	<12										A_6	$12A_6$	$12A_6$	$12A_6$	$12A_6$	$12A_6$
2087	100										A_6	$250A_6$	$250A_6$	A_6	ND†	ND†
2131	125										A_6	$333A_6$	$333A_6$	A_6	$333A_6$	$250A_6$
2134	125B	166	B	125	125B	125	125B	125	100B	125	100		125		166	$250A_6$
2135	250										A_6	333	$625A_6$	333	333	

NOTE:—Blank spaces indicate negative streptococcal cultures; no sera taken at these times.
*L=Beta hemolytic streptococcus isolated, but lost in typing.
†ND=Not done because of parental intervention.

or not the organisms were recovered repeatedly during this period; titer levels generally fell one to three tubes within the period of observation. Titers associated with group C or G organisms followed the same general pattern of elevation and slow decline.

The relationship of ASLO responses to school absences of children from whom beta hemolytic streptococci were isolated, will be discussed in a future communication.

Discussion

Antistreptolysin O titers in the present investigations indicated that 88.7 per cent of children six to nine years of age, sampled in October 1954, already had had at least one infection with a streptolysin O producing organism. This conclusion is based on the concept that any titer of 12 units or greater reflects an immunologic response to streptolysin O.

Since so high a percentage of children did manifest titer elevations, we were faced with the problem of determining how the ASLO titer might assist in evaluation of the effect of the presence of streptococci in the host. This problem must be considered when single titer levels are known, and also, when serial samples are collected.

Study of single ASLO titers in relation to the isolation of various Lancefield groups of beta hemolytic streptococci, as contrasted with titers from those children from whose throats these organisms were not isolated, showed that each bacteriological category was accompanied by an overall range of titers which followed normal curves of distribution; the curve for each group markedly overlapped all other curves. However, titers of less than 12 units were most common when no streptococci were recovered from throat cultures. High titers, 250 units or above, were seen in only 5.6 per cent of children from whom no beta hermolytic streptococci were isolated. Children who harbored Group A or Group C streptococci were more likely to have titers of 250 units or above than those children with other groups. Conversely, low titers did occur in the presence of streptococci, while elevated titers, up to 833 units, were recorded in a few instances in the absence of these organisms.

We believe that the elevated ASLO titers seen in the absence of any beta hemolytic streptococcal isolates may be due to either (a) failure to recover an organism actually present in the throat, or at some other parenteral site in the host, or (b) absence of the organism at the time of culturing, with the serological response occurring to an organism previously present, or (c) an anemnestic response of the host[5,13] to some other organism. Although the distribution curves of ASLO titers show differences, the marked overlap of these curves indicates the limited assistance that an ASLO titer determination on a single serum sample affords in the evaluation of a patient suspected of suffering from illness due to the streptococcus.

Serial ASLO titer changes probably are more helpful. Our serial studies of an outbreak involving group A, type 6 beta hemolytic streptococci indicated that this new organism, when introduced into a population, involved 35 to 50 per cent of the children exposed. Almost all of those who harbored this organism developed a 2-tube or greater rise in ASLO titer, within 2-4 weeks of our initial recovery of the streptococcus. The titer rise was followed by a prompt slight fall, and then a gradual decline toward the baseline value. In the present investigation, not a single elevated titer had returned to its previous level by the end of the period of observation (3½ months after the first group A, type 6 streptococcal isolation). The peak titers were variable, ranging between 250 and 625 units. This range of peak values, in the 17 children who showed serological responses, was obtained regardless of the "pre-epidemic" titers, so that the elevations, in terms of rise by number of tubes, generally was less when initial levels were high than when baseline levels were 50 units or less. The decline in ASLO titers following the initial peak responses occurred despite the continued presence of group A type 6 streptococci in the throats of most of the children over at least 3½ month period of our study of this "epidemic."

Serial ASLO determinations on sera from children from whom various Lancefield types of group A streptococci other than type 6 were found, indicated that the pattern of antibody response was generally the same: a rise of two or more tubes within four weeks, followed by a slow titer fall during a period of many months.

It must be emphasized that group A organisms were not the only streptococci capable of eliciting elevations seen in serial ASLO titer determinations. Similar patterns of rise and fall in ASLO titers occurred in children in response to organisms of groups C and G, although not with the same uniformity as were observed in the group A type 6 "epidemic."

The findings here reported suggest that rising titers indicate the recent introduction into the host of a new strain of streptococcus which is elaborating streptolysin O; consistently elevated or slowly falling titers are more suggestive that the organism has been present in the host at least several weeks. We have concluded that, for the determination of host status, serial ASLO studies are more useful than are single titer observations.

Compariison of ASLO rises with numbers of colonies (Table 2) demonstrated that colony counts were of limited assistance in indicating host titer responses. Since most colony counts were low, ASLO elevations of 2 tubes or greater were more frequent in every bacteriological category studied when the original colonial count was low. However, large numbers of colonies were more likely to be associated with 2-tube titer rises.

ASLO titer determinations are used to assist in the evaluation of host status in rheumatic fever and acute glomerulonephritis;[14] elevated or rising titers are among the minor criteria indicated for guidance in the diagnosis of rheumatic fever.[15] Roy, Sturgis and Massell[16] have reported that 82.7 per cent of 208 patients with rheumatic fever and cardiac involvement of 16 weeks' duration or less had ASLO titers of 400 units or more, and no titer was less than 83 units. Of 227 patients with rheumatic arthritis of 16 weeks' duration or less, only four had titers below 159 units. Over 50 per cent of each of two additional groups of patients, one with rheumatoid arthritis and the other with miscellaneous illnesses involving joints or extremities, had titers below 159 units. The authors conclude that "although a high antistreptolysin-O titer is quite helpful in confirming a diagnosis of rheumatic fever, a very low titer is even more helpful in excluding rheumatic fever." Stollerman and co-workers[17] reported ASLO titers of 250 units or more in 95 per cent of 20 patients within 1 month of onset of rheumatic fever. Such high levels were not maintained: titers dropped below 250 units in 26.5 per cent of 68 patients in two months, in 66.1 per cent of 59 patients in six months, and in 79.5 per cent of 44 patients by the end of one year. Thus ASLO titer levels and responses may assist in the diagnoses of rheumatic fever, but interpretation must be cautious. "An elevated titer is characteristic of, but not diagnostic of or specific for, rheumatic fever."[18]

TABLE 4—ANTISTREPTOLYSIN O RESPONSES TO STREPTOCOCCAL INCIDENTS, 1954-1955

Streptococcal Group	Total No. Incidents	ASLO Response†	Schools K*	C*	D*	Totals	Per cent Incidents Showing ASLO Rise
Group A, typable strains	55	Rise	17	3	6	26	47.3
		No Rise	9	8	12	29	52.7
Group A, non-typable strains	85	Rise	10	12	9	31	36.5
		No Rise	12	8	34	54	63.5
Group B	11	Rise	1	1	0	2	18.2
		No Rise	4	2	3	9	81.8
Group C	41	Rise	1	2	7	10	24.4
		No Rise	6	4	21	31	75.6
Group F	15	Rise	1	0	0	1	6.7
		No Rise	4	2	8	14	93.3
Group G	29	Rise	3	1	1	5	17.2
		No Rise	1	8	15	24	82.8
TOTALS	236	Rise	33	19	23	75	31.8
		No Rise	36	32	93	161	68.2
		Total	69	51	116	236	—
No. of Children	—		61	41	82	184	

*K=Middle income, white school.
C=Low income, white school.
D=Mixed income, negro school.
†Rise=2 tubes or greater.

The small number of cases of rheumatic fever reported in South Florida[8,9] is far below what would be expected if 3 per cent of the children who harbored group A beta hemolytic streptococci and manifested ASLO serum elevations (40.7 per cent of group A incidents in the present study) were to develop acute rheumatic fever episodes. Our present data deal with streptococcal infection rather than with rheumatic fever directly, for none of the children participating in this investigation developed clinical rheumatic fever.

Our studies indicate that ASLO titer levels, whether as single or serial values, furnish limited information and require careful analysis in the evaluation of the host-organism interrelationship and of the etiologic relationship of streptococci to rheumatic fever in the Miami area.

SUMMARY

1. Antistreptolysin O (ASLO) titers of blood drawn from 333 children attending the first three grades of public schools in Miami, Florida, were determined in conjunction with studies of beta hemolytic streptococci isolated from the throats of the same subjects.

2. Forty-eight of 472 blood samples yielded titers of 250 or above; 21 sera had titers of 333 or higher.
3. The overall average titer and indices were 102.5 (average titer), 3.96 (arithmetic index) and 8.08 (modified index). These levels were lowest in the bloods of those children from whose throats no streptococci or only group B organisms were isolated; next higher with groups F and G; still higher with group C; highest with group A organisms, non-typable and typable.
4. ASLO titers of successive blood samples taken from children from whose throats group A beta hemolytic streptococci were isolated, showed a rise of 2 tubes or more in 29.1 per cent of the 55 children with typable strains and 27.0 per cent of the 37 with non-typable strains. A similar rise was demonstrated in 16.7 per cent of the 18 children with group C streptococci, but only 5.1 per cent of the 99 children from whom no beta hemolytic streptococci were isolated.
5. Sera from 66 children who participated in both this investigation and in a study during the previous year, revealed higher average ASLO titers and indices in the second year (1954-1955) than in the first (1953-1954).
6. High colony counts on original isolation plates were more likely to be associated with a 2-tube or greater ASLO titer elevation, than were low colony counts.
7. The value of single and of serial ASLO titer determinations was considered for the estimation of host status. These serological data furnish limited information and require careful analysis in the evaluation of host-organism interrelationship and of the etiologic relationship of beta hemolytic streptococci to rheumatic fever in the Miami area.

ACKNOWLEDGMENT: We gratefully acknowledge the cooperation of Dr. Robert E. Serfling, Chief of the Statistics Section, Epidemiology Branch, Communicable Disease Center, Atlanta, Georgia, in the calculation of the modified ASLO index.

RESUMEN

1. Los títulos de antestreptolisina O (ASLO) encontrados en la sangre extraída de 333 niños que asisten a los primeros tres grados de las escuelas públicas de Miami, Florida, se determinaron al mismo tiempo que se estudiaron los estreptococos beta hemolíticos aislados de las gargantes de los mismos niños.
2. El cuarenta y ocho por ciento de 472 muestras de sangre, mostraron títulos de 250 o más; 21 sueros dieron títulos de 333 o más altos.
3. En general, el título medio y los índices fueron 102.5 (título medio), 3.96 (índice aritmético) y 8.08 (índice modificado). Estos niveles fueron más bajos en las sangres de los niños en quienes no se encontraron en sus gargantes estreptococos o sólo se aislaron organismos del grupo B. Los grupos que siguieron, fueron en frecuencia los F y G; aún más altos lo fueron con el grupo C; el mayor fué con grupo A de organismos no tipificados o tipificados.
4. Las muestras de sangre sucesivas con respecto a ASLO, tomadas de niños en cuyas faringes había estreptococo betahemolítico, mostraron una elevación de dos tubos o más en 29.1 por ciento de 55 niños con cepas identificables y 27 por ciento de 37 con cepas no identificables en cuanto a su tipo. Una elevacièn similar se demostró en 16.7 por ciento de 18 niños con estreptococo grupo C, pero sólo 5.1 por ciento de 99 niños en quienes no se aisló estreptococo hemolítico beta.
5. Los sueros de 66 niños que participaron en esta investigación y en el estudio en el año anterior, revelaron más alto título medio de ASLO e índices en el segundo años (1954-1955) que en el primero (1953-1954).
6. Hubo más coincidencia de cuentas elevadas en las colonias de altas placas originales con los 2 tubos o una mayor titulación de ASLO que cuando se trató de bajas cuentas en las colonias.
7. El valor de las determinaciones únicas o en serie de ASLO, hubo de considerarse para estimar las condiciones del huésped. Estos datos serológico dan una información limitada y requieren un análisis cuidadoso para la valuación del estreptococo hemolítico en la fiebre reumática en el área de Miami, Florida.

RESUMÉ

1. Le dosage des antistreptolysines O dans le sang de 333 enfants fréquentant les classes des trois premiers degrés des écoles publiques de Miami (Floride) a été pratiqué en même temps que l'étude des streptocoques hémolytiques béta isolés à partir du pharynx des mêmes sujets.
2. 48 des 472 échantillons sanguins donnèrent des titres de 250 et au-dèssus; 21 de 333 et plus.
3. Le titrage moyen global et les indices furent de 102,5 (dosage moyen) 3,96 (index arithmétique) et 8,08 (index modifié). Les taux furent les plus bas dans le sang des enfants dont la gorge ne contenait pas de streptocoques ou dont on ne put isoler que des germes du groupe B; une moyenne plus élevée fut obtenue pour les groupes F et G; un dosage encore plus élevé pour le groupe C; la moyenne la plus élevée fut celle concernant les microbes du groupe A, qu'on puisse les typer ou non.

4. Les titres des antistreptolysines O des échantillons sanguins isolés de façon répétée chez les enfants dont la gorge contenait des streptocoques hémolytiques du groupe A beta, montrèrent une augmentation de deux tubes ou même davantage pour 29,1% des 55 enfants porteurs de souches qui purent être typées et 27% pour 37 enfants porteurs de souches qui ne purent être typées. Une augmentation semblable fut mise en évidence dans 16,7% d'un groupe de 18 enfants porteurs de streptocoques du groupe C, mais de telles constatations ne concernèrent que 5,1% des 99 enfants pour lesquels on ne put isoler aucun streptocoque hémolytique beta.
5. Le sérum de 66 enfants qui participaient à la fois aux investigations présentes et à l'étude faite l'année antérieure, révélèrent une moyenne plus élevée des titres des antistreptolysines O et des indices pour la seconde année (1954-55) que pour la première (1953-54).
6. L'existence d'un nombre élevé de colonies sur le premier milieu ou a été faite la culture semblait plus souvent liée à une élévation du taux des antistreptolysines de deux tubes ou plus que lorsque le nombre des colonies avait été plus limité.
7. La valeur de la mise en évidence des antistreptolysines O soit par une seule investigation soit par investigations successives fut prise en considération pour évaluer la condition de l'individu chez qui les dosages étaient effectués. Ces données sérologiques fournissent une information limitée et nécessitent une analyse prudente dans l'évaluation des relations hôte-agent microbien et du rapport étiologique qui unit les streptocoques hémolytiques beta et le rhumatisme articulaire dans la région de Miami.

ZUSAMMENFASSUNG

1. Es wurden die Antistreptolysin-O (ASLO) — Titer im Blut bestimmt bei 333 Kinder der ersten 3 Klassen der öffentlichen Schulen von Miami in Florida und zwar in Verbindung mit Untersuchung der beta-hämolytischen Streptokokken von Rachenabstrichen derselben Kinder.
2. 48 von 472 Blutproben ergaben Titerwerte von 250 oder mehr; 21 Seren hatten Titer von 333 oder höher.
3. Die Durchschnittswerte für die gesamten Titer und Indices lagen bei 102,5 (Durchschnittstiter), 3,96 (arithmetisscher Index) und 8,08 (modifizierter Index). Diese werte waren am niedrigsten im Blut derjenigen Kinder, deren Rachen keine Streptokokken oder nur solche mit Organismen der B-Gruppe isoliert worden waren; nächst höher waren dieffienigen mit den Gruppen F und G; noch höher mit der Gruppe C und am höchsten mit Erregern der Gruppe A, der nicht typischen und der typisierbaren.
4. ASLO-Titer von aufeinanderfolgenden Blutproben bei Kindern, aus deren Halsabstrichen beta-hämolytische Streptokokken der Gruppe A isoliert worden waren, zeigten einen Anstieg von 2 Röhrchen oder mehr bei 29,1% der 55 Kinder mit Stämmen deren Typen bestimmbar waren und 27,0% der 37 nicht typisierbaren Stämme. Ein ähnlicher Anstieg liess sich nachweisen bei 16,7% der 18 Kinder mit Streptokokken der Gruppe C, aber nur 5,1% der 99 Kinder, bei denen keine beta-hämolytischen Streptokokken gewonnen worden waren.
5. Die Seren von 66 Kindern, die sowohl an dieser Untersuchungsreihe wie an der während des vergangenen Jahres teilgenommen hatten, ergaben höhere durchschnittliche ASLO-Titer und Indices im 2. Jahr (1954/1955) als im ersten Jahr (1953/1954).
6. Von hohen Koloniezahlen bei der ursprünglichen Isolierungskultur war es wahrscheinlicher, dass sie zusammen vorkamen mit einem ASLO-Titer-Anstieg von 2 oder mehr Röhrchen, als wenn die Zahl der Kolonien niedrig lag.
7. Die Zahlen für einzelne oder Reihen-ASLO-Titerbestimmungen wurden hinsichtlich ihres Wertes für den Status des Wirtes geprüft. Diese serologischen Daten bringen nur eine begrenzte Information und enfordern sorgfältige Analysen bei der Bewertung der Wechselwirkung zwischen Wirt und Erreger und der ätiologischen Beziehung von beta-hämolytischen Streptokokken zum rheumatischen Fieber im Gebiet von Miami.

REFERENCES

1 Dingle, J. H., Abernethy, T. J., Badger, G. F., Beard, J. W., Cressy, N. L., Feller, A. E., Gordon, I., Langmuir, A. D., Rammelkamp, C. H., Jr., Strauss, E., and Tetlock, H.: "Role of Beta Hemolytic Streptococci in Common Respiratory Disease," *Am. J. Pub. Health*, 35:675, 1945.

2 Rammelkamp, C. H., Jr.; Wannamaker, L. W., and Denny, F. W.: "The Epidemiology and Prevention of Rheumatic Fever," *Bull. New York Acad. Med.* 28:321, 1952.

3 Saslaw, M. S., and Streitfeld, M. M.: "Group A Beta Hemolytic Streptococci and Rheumatic Fever in Miami, Fla." A Preliminary Report. *Pub. Health Repts.* 69:877, 1954.

4 Streitfeld, M. M.; Saslaw, M. S., and Doff, S. D.: "Group A Beta Hemolytic Streptococcus and Rheumatic Fever in Miami, Fla." 8-month Bacteriological and Serologic Study. *Pub. Health Repts.* 71:745, 1956.

5 Saslaw, M. S., and Streitfeld, M. M.: "Group A Beta Hemolytic Streptococci in Relation to Rheumatic Fever." Study of School Children in Miami, Fla. *A.M.A. J. Dis. Child.*, 92:550, 1956.

6 Saslaw, M. S., and Streitfeld, M. M.: "Group A Beta Hemolytic Streptococci and Rheumatic Fever in Miami, Fla. Bacteriologic Observations from October 1954 through May 1955," submitted for publication.

7 Streitfeld, M. M., and Saslaw, M. S.: "Streptococci and Rheumatic Fever. Influence of Age of Population on the Recovery and the Antistreptolysin O Serological Response," presented at the 5th Inter-American Congress of Cardiology, Havana, Cuba, Nov. 12, 1956.

8 Saslaw, M. S.; Ross, B. D., and Dobrin, M.: "The Incidence of Rheumatic Heart Disease in Native School Children of Dade County, Florida." *Am. Heart J.* 40:760, 1950.

9 Saslaw, M. S.: "Case Registry for Rheumatic Fever and Glomerulonephritis." *J. A.M.A.*, 1957, accepted for publication.

10 Rammelkamp, C. H., Jr.: "Prevention of Rheumatic Fever." *Bull. on Rheumatic Diseases*, 2:13, 1952.

11 Rantz, L. A., and Randall, E.: "A Modification of the Technique for the Determination of the Antistreptolysin Titer." *Proc. Soc. Exper. Biol. and Med.* 59:22, 1945.

12 Saslaw, M. S.; Streitfeld, M. M., and Williams, E. H., Jr.: "Use of an Antistreptolysin-O Index for Comparison of Large Samples: Experience in Miami, Florida." *Clin. Research Proc.*, 3:77, 1955.

13 Kupatz, H., and Koehler, W.: "Antistreptolysin Reaction in Disease of Childhood." *Monatsschr. Kinderh.*, 103:415, 1955, *Abst.* in *A.M.A. J. Dis. Child.*, 92:409, 1956.

14 Adams, F. H.: "An Appraisal of Certain Acute Phase Reactants in a Single Blood Sample and Their Value in the Diagnosis of Acute Rheumatic Fever." *J. Pediat.* 49: 16, 1956.

15 Rutstein, D. D., Bauer, W., Dorfman, A., Gross, R. E., Lichty, J. A., Taussig, H. B., and Whittemore, R.: "Jones Criteria (modified) for Guidance in the Diagnosis of Rheumatic Fever." *Md. Concept. Cardiovas. Dis.* 24:291, 1955.

16 Roy, S. B.; Sturgis, G. P., and Massell, B. F.: "Application of the Antistreptolysin-O Titer in the Evaluation of Joint Pain and in the Diagnosis of Rheumatic Fever." *New England J. Med.*, 254:95, 1956.

17 Stollerman, G. H.; Lewis, A. J.; Schultz, I., and Taranta, A.: "Relationship of Immune Response to Group A Streptococci in the Course of Acute, Chronic and Recurrent Rheumatic Fever." *Am. J. Med.* 20:163, 1956.

18 Robinson, W. D., Bunim, J. J., Clark, W. S., Crain, D. C., Engleman, E. P., Graham, D. C., Montgomery, M. M., Norcross, B. M., Ragan, C., Ropes, M. W., Rosenberg, E. F., and Smyth, C. J.: "Rheumatism and Arthritis. Review of American and English Literature of Recent Years" (Eleventh Rheumatism Review). *Ann. Int. Med.* 45:831, 1956.

Effect of Intermittent Positive Pressure Breathing on the Cardiac Output of Patients with Chronic Pulmonary Disease*, **

RICHARD T. CATHCART, M.D., WILLIAM FRAIMOW, M.D.
THOMAS F. NEALON, JR., M.D., F.C.C.P., and JOYCE PRICE, R.N.
Philadelphia, Pennsylvania

The effect of various intermittent positive pressure breathing devices on cardiac output has been studied by Motley[1] in a group of normal patients. He found that decreases in cardiac output were directly related to the height of the mean mask pressure. It was part of his conclusion that intermittent positive pressure breathing could be used without decreasing cardiac output when the pressures were properly regulated. Maloney,[2,3] however, has pointed out the possible harmful effects of intermittent positive pressure type respirators. He has indicated that in patients with respiratory and/or circulatory failure these effects might be life threatening.

At present the effects of IPPB on the large group of patients who are neither normal nor have circulatory insufficiency have not been fully delineated and are subject to controversy. In recent years IPPB has become a more frequently employed and generally accepted form of therapy in the treatment of severe pulmonary emphysema. Because of this it appeared to us almost imperative that an appreciation of the effects of IPPB on this group of patients should be available. It would seem that in order to relate changes in cardiac output to the therapeutic situation more than a quantitative estimation of drop in cardiac output was necessary. Specifically it was hoped to make serial determinations of cardiac output. In this way the duration of therapy could be evaluated and in addition, the recovery phase following cessation of treatment could be explored. The dye dilution technique with its present modification offered an excellent method of making such repeated measurements.[4-7]

Methods and Materials

Thirty-one men were studied. Their ages ranged from 24 years to 70 years with an average age of 58 years. All had pulmonary emphysema, pulmonary fibrosis, or other diffuse pulmonary pathology. Twenty-eight had pulmonary emphysema associated with anthracosilicosis. All had been well trained and were completely familiar with the efficient use of the particular IPPB device used† (Table 1).

The cardiac outputs were determined by an indicator dilution technique using a measured dose of approximately 5 mgm. of T-1824. The dye was introduced through a polyethylene catheter with an outside diameter of 1.22 mm. and an inside diameter of 0.76 mm. which had

*From the Departments of Medicine and Surgery, Jefferson Medical College. This work was supported by the Anthracite Health and Welfare Fund.
**Presented in part at the 24th Annual Meeting, American College of Chest Physicians, San Francisco, June 18-22, 1958.
†Pulmonary Ventilator, Mine Safety Appliance Company, Pittsburgh, Pa.

TABLE 1

Patient	Age	Control Period 100 per cent O_2 Breathing			After 10 Minutes of IPPB O_2 Breathing				After 20 Minutes of IPPB O_2 Breathing				Recovery—(10 Minutes After IPPB Was Stopped)			
		Pulse	Blood Pressure	Cardiac Output L/Min.	Pulse	Blood Pressure	Cardiac Output L/Min.	Per Cent Change from Control	Pulse	Blood Pressure	Cardiac Output L/Min.	Per Cent Change from Control	Pulse	Blood Pressure	Cardiac Output L/Min.	Per Cent Change from Control
1.	49			5.77							5.42	−6				
2.	66	70		4.34	66		3.27	−25								
3.	64	48		2.86	52		2.34	−18	52		2.81	−2				
4.	58	60		4.71					58		4.29	−9				
5.	70	80		3.30	78		2.91	−12	76		2.79	−15				
6.	63	82		4.00	90		3.90	−3								
7.	65	60		4.73	64		4.25	−10	66		4.51	−5				
8.	24	66		5.43	68		4.60	−15								
9.	55	73		3.67	72		3.86	+5								
10.	65	73		4.16	80		4.12	−1	78		3.89	−6				
11.	38	90		8.24	84		8.30	+1								
12.	42	56		3.47	48		3.16	−9	55		2.38	−31				
13.	62	56		3.28	56		2.70	−16	56		2.72	−15				
14.	66			3.35			3.40	−9								
15.	55	98	110/76	5.81	96	114/74	6.15	+6	96	108/82	6.45	+11	92	118/76	6.96	+20
16.	55			4.10					76	112/70	2.93	−29				
17.	68	68	90/60	4.00					64	98/64	3.38	−16			3.96	−1
18.	69	88	120/78	2.99					84	108/70	2.49	−17	84	110/74	3.07	+3
19.	65	76	120/80	3.20	84	106/72	2.50	−22	84	108/70	2.64	−18	80	120/80	3.85	+20
20.	63	72	110/70	3.14	80	110/80	2.88	−8	76	106/90	2.65	−16	80	118/98	2.96	−6
21.	69	76	116/80	4.48					76	124/82	3.99	−11			4.54	+1
22.	65	60	110/70	4.03	62	102/66	3.66	−9	64	102/64	3.72	−8	64	112/72	4.09	+1
23.	61	78	130/86	2.07	88	110/94	1.57	−24	92	110/80	1.63	−21	80	130/90	2.13	+3
24.	47	108	118/70	6.95	102	112/74	7.37	+6	96	106/76	7.31	+5				
25.	66	78	126/78	3.17					80	118/76	2.32	−27	82	140/82	3.23	+2
26.	48			4.65	68	112/80	4.00	−14	64	110/80	3.84	−17	64	108/28	3.84	−17
27.	57	64	138/94	3.54	64	134/100	3.77	+6		140/100	3.56	+1	62	140/94	3.68	+4
28.	61	62	136/68	4.13	64	122/100	3.96	−4	60	124/74	3.56	−14	64	128/72	4.52	+9
29.*	50	74	114/74	3.36	80	108/74	3.09	−8	84	92/60	2.65	−21	78	94/60	3.46	+3
30.	60	80	162/80	4.29	88	168/92	3.18	−26	80	150/92	3.02	−30	74	148/88	3.65	−15
31.	55	56	146/88	3.44	58	144/76	3.39	−1	54	140/80	3.08	−10	56	156/76	3.90	+13

*Auricular fibrillation present

been inserted percutaneously into an antecubital vein and threaded up to the subclavian vein. The catheter was attached to a three-way stopcock and physiological saline was dripped in slowly to keep the catheter patent. Following rapid injection of the dye the catheter was flushed with 10 cc. of saline to assure delivery of the dye as a bolus.

A Cournand needle was inserted percutaneously into a brachial artery. When not in use the standard occluding stylet was left in place. When in use the needle was connected to a cuvette densitometer† by a short piece of polyethylene tubing with an outside diameter of 1.57 mm. and an inside diameter of 1.14 mm. Special adapters assured airtight connections. From the densitometer cuvette the arterial blood then passed via another short piece of polyethylene tubing into a collecting chamber which had a constant negative pressure of approximately 22 cm. of water. A solenoid switch inside the chamber permitted selective sampling of the blood by moving a test tube beneath the stream of incoming blood without interrupting the flow.[8] A simultaneous marker allowed us to use this integrated sample for calibration of the dye curve. The dye curve was visualized and photographically recorded on a multiple channel oscillograph. (Fig. 1)

†Colson Densitometer, Colson Company, Elyria, Ohio

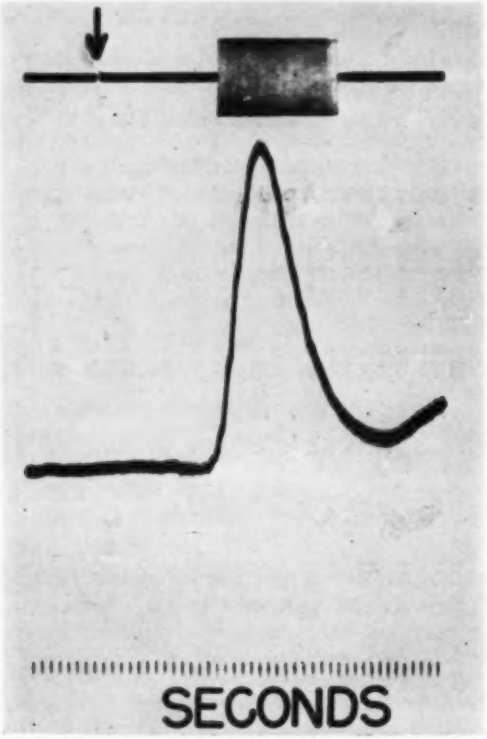


FIGURE 1 Typical dye dilution curve. The arrow indicates the time of injection. The broadened beam signifies time interval during which blood-dye sample is collected.

A control sample of arterial blood was first drawn and the arterial needle was then connected to the cuvette. The wedge shielding the photoelectric cell in the densitometer was withdrawn and the densitometer gauge adjusted to 0. Satisfactory base lines depended on steady bubble-free flow and could be adversely affected by variation in the degree of arterial O_2 saturation. Following the injection of dye, the solenoid switch was activated to collect blood in the test tube during the inscription of the curve and simultaneously mark the exact period of collection. The concentration of dye in the integrated sample of blood was measured against its blank in a Beckman Model D.U. Spectrophotometer. The cardiac output was then calculated from the formula $F = \frac{I}{C\,T}$, where F equals flow or cardiac output, I represents the amount of indicator substance injected, C represents the mean concentration, and T represents the time.[7]

The patients in a resting state were placed in a supine position on the table. They were then permitted to breathe 100 per cent O_2 by mask. At the end of 10 minutes a control cardiac output determination was made. A second control measurement was made after another 10 minute interval. Oxygen was used as the breathing mixture for two reasons: (1) to obviate the differences that might arise from the subsequent administration of 100 per cent O_2 by the IPPB device and (2) to prevent artefacts

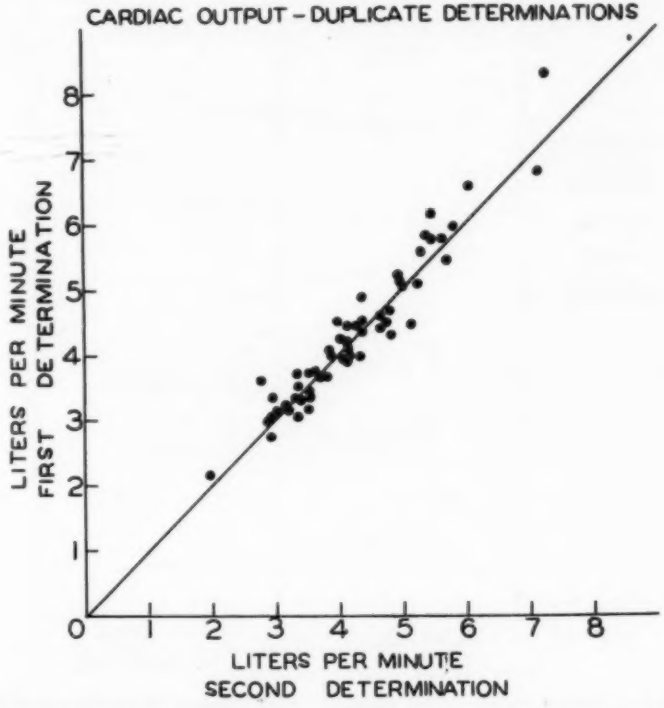


FIGURE 2 Duplicate determinations of cardiac output on 56 patients under identical circumstances.

in the inscription of the curve which might arise as the result of anoxemia. Immediately after the second measurement, the patient was placed on an IPPB apparatus and cardiac outputs were determined 10 and/or 20 minutes later. Subsequent determinations were made 10 minutes after IPP breathing had been discontinued, but with 100 per cent oxygen still the inspired gas. In all cases the peak pressure setting of the apparatus was 20 cm. H_2O. Simultaneous pressure curves were recorded in typical cases and the mean mask pressure was measured planimetrically. Pulse rates were recorded at the time of the cardiac output determinations. Arterial pressures were measured with a sphygmomanometer. Peripheral resistance was calculated from the formula:

$$\text{Resistance} = \frac{\text{Mean Arterial Pressure in mm. Hg.}}{\text{Cardiac Output in cm}^3 \text{ per second}} \times 1332$$

The mean pressure was assumed to be the diastolic pressure plus one third of the pulse pressure.

Results

In order to establish the precision and reproducibility of the dye dilution technique in our laboratory, a series of duplicate measurements

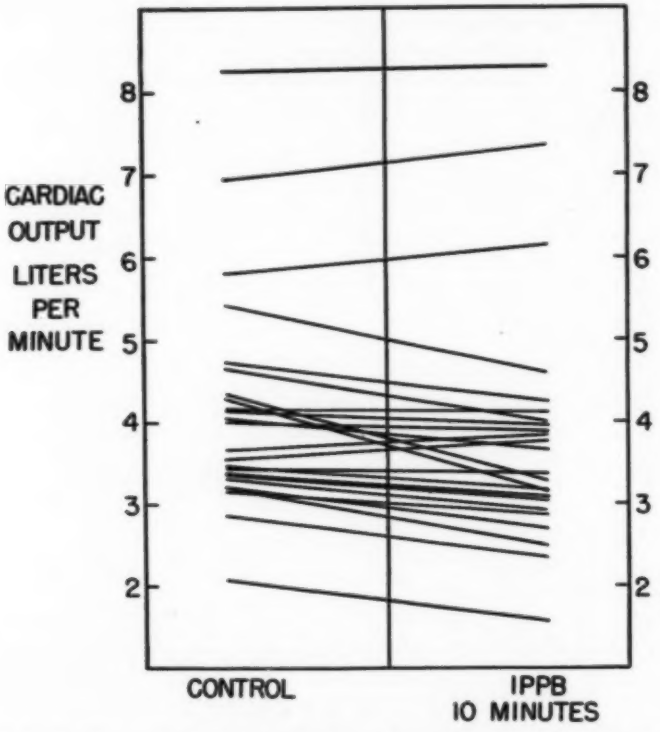


FIGURE 3 Cardiac output of 24 patients under resting conditions breathing 100 per cent oxygen and after 10 minutes of intermittent positive pressure oxygen breathing.

was performed. In all, 112 determinations were made under similar conditions in a group of 56 patients. These are depicted in Fig. 2. Of the 56 points, 48 (86 per cent) fellt within ±10 per cent of identity while 55 or 98 per cent fell within ±13 per cent. Of importance also is the even scatter of the results about the line of identity. The standard deviation, a measure of the degree of variation between duplicate determinations, was 0.21*.

*Computed as follows: Standard Deviation $= \sigma = \sqrt{\frac{\Sigma d^2}{2N}}$

Where d is the difference between the two determinations on a given patient and N is the number of patients on whom duplicate determinations were made. (Youden, W. J.: *Statistical Methods for Chemists*, John Wiley & Sons, New York, June 1955, p. 16.)

In a group of 24 subjects (Fig. 3) who received intermittent positive pressure breathing at 20 cm. H_2O for a period of 10 minutes, a fall in cardiac output was noted in 21 (87.5 per cent). Nine cases (37.5 per cent) showed a fall of more than 10 per cent and 25 per cent (6 cases) showed a fall of more than 15 per cent. For the group as a whole the range of change was from +6 per cent to −26 per cent with an average of −9.3 per cent. A plot of the cardiac output values in these subjects before and after treatment is shown in Fig. 4.

In a group of 25 patients (some of whom were included in the preceding group) IPPB was given for a period of 20 minutes (Fig. 5). Similar,

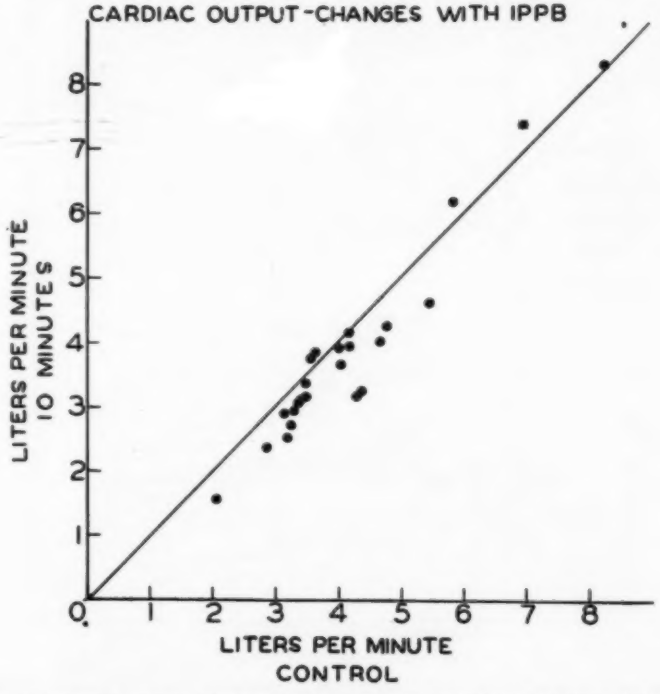


FIGURE 4 Cardiac output determinations after 10 minutes of intermittent positive pressure breathing plotted against control values.

but slightly greater changes were observed. A fall in cardiac output occurred in 22 (88 per cent). Fifty-six per cent (14 cases) showed a fall of more than 10 per cent and 40 per cent (10 cases) showed a fall of more than 15 per cent. The average change in cardiac output was −12 per cent with a range from +11 per cent to −31 per cent. Fig. 6 is a plot of the determinations made in this group before and after using IPPB.

Measurements were made in the recovery phase upon four patients who received IPPB for 20 minutes. The initial decreases in cardiac output ranged from 11 per cent to 27 per cent. In all cases the output measurements were found to be at control levels 10 minutes after cessation of treatment.

In 11 cases it was possible to measure the cardiac output at control levels, after 10 minutes of IPPB, after 20 minutes and finally 10 minutes after cessation of treatment (Fig. 7). Nine of the 11 (82 per cent) showed a fall in cardiac output, the range of fall being −1 per cent to −30 per cent with an average change of −12.5 per cent. Of those cases where a fall in cardiac output was observed, all but three had completely recovered within 10 minutes after the end of treatment. Of these three subjects, two had shown recoveries of 50 to 70 per cent respectively after 10 minutes and in only one instance was there no recovery. After 10 minutes there was an average fall of 8.4 per cent and after 20 minutes

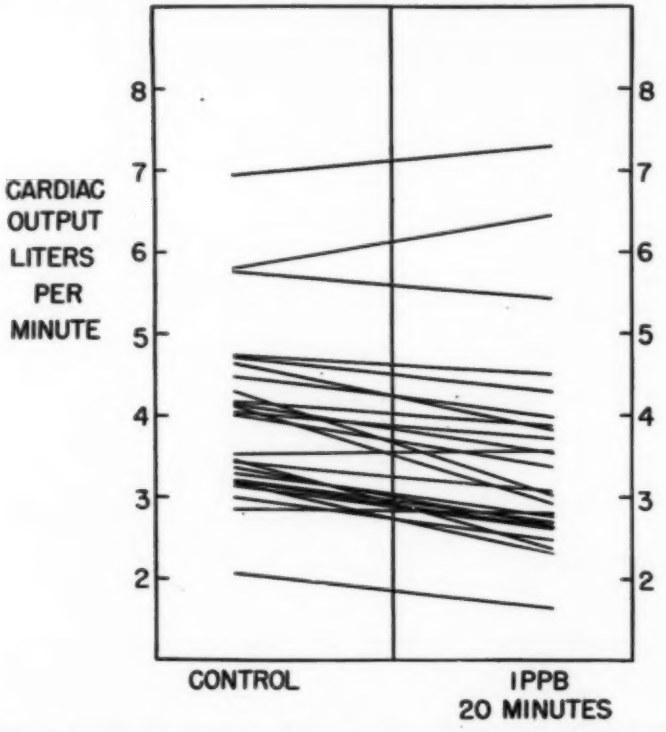


FIGURE 5 Cardiac output of 25 patients at resting conditions and after 20 minutes of intermittent positive pressure breathing.

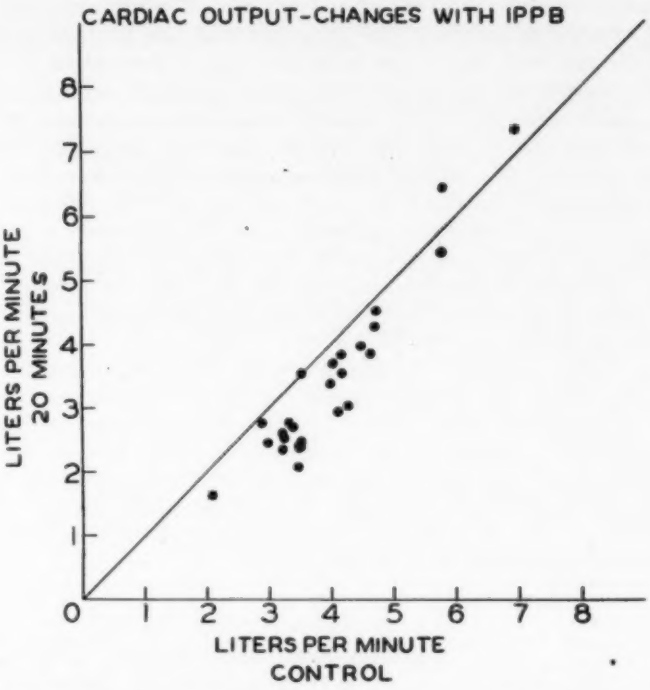


FIGURE 6 Cardiac output determinations after 20 minutes of intermittent positive pressure breathing plotted against control values.

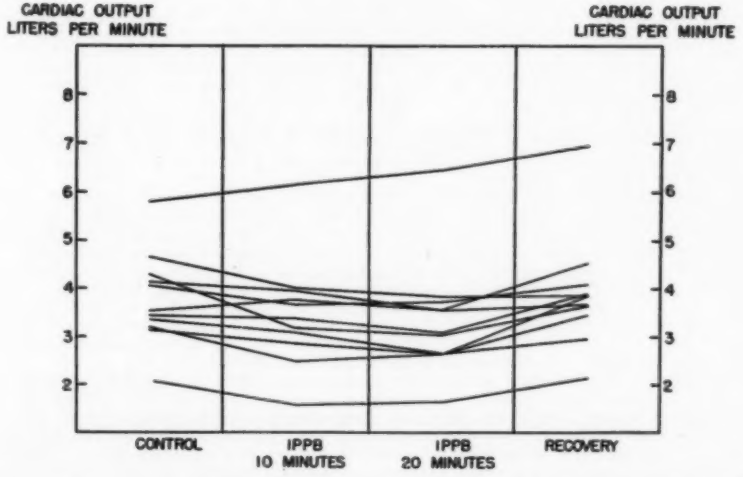


FIGURE 7 Cardiac output determinations of 11 patients under resting conditions, after 10 minutes of intermittent positive pressure breathing, 20 minutes of intermittent positive pressure breathing and during recovery period.

a somewhat more marked fall of 11.6 per cent. Ten minutes after cessation of treatment recovery was complete and the average values for cardiac output were some 3 per cent in excess of the control level.

Blood pressure measurements showed no consistent trend which could be correlated with changes in cardiac output. The maximum change in blood pressure was 20 mm. Hg. systolic, and was associated with a 24 per cent fall in cardiac output. Alterations in heart rate were not marked and showed no consistent trend in response to IPPB. Stroke volume, on the other hand, tended to fall and except for rare instances the fall in cardiac output observed was indeed a reflection of a decrease in stroke volume. Changes in peripheral resistance were not striking. However, it was noted in all cases where there was a fall in cardiac output, a rise in peripheral resistance was calculated.

The appearance time of the dye in the blood stream ranged from nine to 21 seconds with an average time of 14.2 seconds. Changes in cardiac output were unassociated with alteration in appearance time as had been suggested[9]. Change in appearance time could not be correlated with the phase of the respiratory cycle in which the dye was injected.

The mean mask pressure ranged from +3 to +6 cm. of H_2O with an average of +5 cm. H_2O. At these pressures no adverse clinical effects accompanied changes in cardiac output.

Discussion

That increased intrathoracic pressure might cause circulatory effects has been reported as early as 1851 by Weber[10] who noted the disappearance of the heart beat and arterial pulse. Indeed, the use of the Valsalva maneuver to differentiate patients with heart failure and valvular disease from normal patients on the basis of its circulatory effects has been advocated and employed by many.[1-14] The basis for the changed output in normal man is most intimately related to the dynamics of the right side of the heart. As the intrathoracic pressure is increased, filling of the right side of the heart from the large veins is reduced and the stroke volume diminished. Output from the left side of the heart will actually increase for three to five beats as a result of increased pulmonary venous return, but then fall because of decreased output of the right side of the heart.[15] With IPPB the phase of rising intrathoracic pressure occurs with inspiration and the phase of decreasing pressure occurs with expiration. This is the opposite of the situation as occurs in normal respiration. Others[16] have shown that positive pressure does not obstruct blood flow through the pulmonary vascular bed any more than does the same degree of inflation occurring during normal inspiration. This then further confirms that the main effect of increased intrathoracic pressure is one of tamponade with interference of venous return. With the reduction in net filling pressure the stroke volume of the right heart is reduced, as would be expected from Starling's law. This results ultimately in diminution of the left heart output.

The increased use of IPPB devices as a therapeutic measure in pulmonary emphysema has caused us to evaluate their effects on cardiac output in this group of patients. Earlier work with normal subjects and with those in circulatory failure has shown divergent results in these groups regarding changes in cardiac output.[1-3,17-19] More important, these studies have not related the changes to the emphysematous patients, the particular group in which these devices are most frequently utilized today. Seldom is a single treatment with IPPB life-saving and it is ordinarily used repeatedly in the emphysematous patient. Its role as an adjunct therapy in a chronic disease state, therefore, demands a keen appreciation of any possible deleterious effects on circulation in order to properly evaluate its usefulness.

Although it is known that in an hypoxic subject oxygen will decrease the cardiac output, it appears unlikely that the changes in output observed in this study were the result of oxygen breathing. The two control determinations were made after 10 and 20 minutes of oxygen breathing before IPPB was begun and no fall in output occurred. Furthermore, there was a return to control values when positive pressure breathing was discontinued, even though the subjects continued to breathe oxygen.

Our observations indicate that changes in cardiac output were small but consistent in direction and the result of the use of intermittent positive pressure. If treatment really had no effect, one would expect approximately one half to show decreases. The probability of five or fewer changes in a given direction in 24 patients is less than

0.01 while the probability of three or fewer changes in a given direction in 25 patients is less than 0.001. It must be concluded, therefore, that whether IPPB is given for 10 or 20 minutes, there is a fall in cardiac output which while rather modest is statistically highly significant.

Clinical experience has shown that dire results are not usually associated with the use of IPPB in the ordinary therapeutic regimen. Our data confirms and helps to explain this. While we have observed a definite and almost uniform decrease in cardiac output with intermittent positive pressure breathing, these changes have been small. Moreover, these changes were in the range where detrimental results would not be expected. Of particular importance is the observation that cardiac output returns to normal and indeed even above normal values promptly following the cessation of therapy. At this point it is impossible to delineate the exact role that time plays in the changes in output and further investigation is proceeding. The body's homeostatic mechanisms which are called into play may have permitted a return of the output to normal values within the time interval studied without the discontinuation of IPPB. On the other hand, the slightly more pronounced drop after 20 minutes may indicate a greater decline in output with longer periods of therapy. The severely ill, emphysematous patient, who requires prolonged periods of therapy, is more prone to suffer drops in cardiac output because of accompanying vasomotor instability. Because of this, it is important that the effect of duration of treatment be more precisely defined.

The ability to call forth normal homeostatic mechanisms to compensate for decreased venous return will predicate the patient's response to IPPB. In the normal individual this response is mediated through vasoconstriction, mobilization of pooled blood and elevation of venous pressure until venous return to the heart is restored. Vasoconstriction was indicated in our patients by the uniform increase in peripheral arterial resistance accompanying falls in cardiac output. This would be expected, noting the vasoconstriction which occurs during the rebound phase of the normal performance of the Valsalva maneuver with its overshoot in arterial pressure.[20] In Maloney's patients with circulatory insufficiency these homeostatic mechanisms had been severely compromised and the patients were no longer able to respond to the stress of decreased venous return. Indeed, our own experiences[21] with patients under anesthesia would tend to show that the suppression of normal mechanisms plays a role in the more profound depression of cardiac output associated with increased endotracheal pressure observed in some patients. These patients were also unable to return to control levels as promptly as the patients we are now reporting. For this reason, we and many others have felt that the incorporation of a negative pressure phase in anesthetized patients with closed chests is desirable in order to maintain adequate ventilation with minimal interference with circulatory dynamics.

A mean mask pressure as close to atmospheric as possible has been advocated to prevent alterations in cardiac output. Due to variations in individual breathing patterns and rates it is impossible to pre-set the mean mask pressure. Accordingly, a peak pressure setting of 20 cm. H_2O was used throughout the study. This resulted in a mean mask pressure ranging from +3 to +6 cm. H_2O. This peak pressure was arbitrarily selected as the maximum pressure used during the normal treatment program. By the selection of this particular peak pressure we have hoped to include all possible changes in cardiac output resulting from the clinical application of IPPB in the emphysematous patient.

CONCLUSION

1. The fall in cardiac output associated with intermittent positive pressure breathing would appear to be definite.

2. With a peak pressure setting of 20 cm. H_2O, these changes do not appear to be of sufficient magnitude to effect adversely the group of patients studied.

3. Upon cessation of treatment, the recovery of cardiac output is both prompt and complete.

4. The magnitude of the changes noted, as well as their transiency, would suggest that intermittent positive pressure breathing as used in this study was associated with no deleterious effect in the uncomplicated case of advanced pulmonary emphysema.

CONCLUSION

1. Parecería que hay un caída en el rendimiento cardiaco cuando se usa la respiración con presión positiva intermitente.

2. Con una presión máxima de 20 cms. de agua al empezar, estos cambios no parece que sean de suficiente magnitud para afectar de modo adverso a los enfermos estudiados.

3. Al cesar el tratamiento, la recuperación del rendimiento cardiaco es pronta y completa.

4. La magnitud de los cambios observados, así como su fugacidad sugerirían que la respiración positiva intermitente tal como se usó en este estudio, no se asocia con efectos dañosos en el caso de enfisema pulmonar avanzado no complicado.

ACKNOWLEDGMENT: The authors are indebted to Dr. Hyman Menduke, Assistant Professor of Biostatistics, Jefferson Medical College, for the statistical analysis and to Mrs. Helen Kelley for her technical assistance.

RESUMÉ

1. La chute du débit cardiaque associé à une respiration intermittente en pression positive semblerait être déterminée.
2. Avec un clocher de pression atteignant 20 cm. d'eau, ces modifications ne semblent pas d'une amplitude suffisante pour affecter le groupe des malades étudiés.
3. Après cessation du traitement, le retour du débit cardiaque est à la fois rapide et complet.
4. L'amplitude des modifications notées, aussi bien que leur durée transitoire, ferait penser qu'une respiration en pression positive intermittente, comme elle est utilisée dans cette étude, n'entraine aucune manifestation fâcheuse dans le cas d'emphysème pulmonaire grave sans complications.

ZUSAMMENFASSUNG

1. Das Absinken des Schlagvolumens des Herzens in Verbindung mit der intermittierenden positiven Druckatmung scheint definitiv zu sein.
2. Bei einer höchsten Drucklinie von 20 mm H_2O scheinen diese Veränderungen nicht genügend gross zu sein, um ungünstige Wirkungen unter der beobachteten Patientengruppe zu bewirken.
3. Bei beendigter Behandlung ist die Normalisierung des Herzschlagvolumens vollständig und prompt.
4. Das Ausmass der beobachteten Veränderungen und ebenso deren Flüchtigkeit legen die Vermutung nahe, dass die intermittierende positive Druckatmung in der bei dieser Untersuchung verwandten Form mit keinerlei nachteiliger Wirkung verknüpft ist bei einem unkomplizierten Fall eines fortgeschrittenen Lungenemphysems.

REFERENCES

1 Motley, H. L.; Cournand, A.; Werko, L.; Dresdale, D. T.; Himmelstein, A., and Richards, D. W., Jr.: "Intermittent Positive Pressure Breathing: A Means of Administering Artificial Respiration in Man," *J.A.M.A.*, 137:370, 1948.

2 Maloney, J. V., Jr., and Handford, S. W.: "Comparison of Circulatory Effects of Intermittent Positive and Positive-Negative Type Resuscitators," Abstracted in *Am. J. Physiol.*, 167:807, 1951.

3 Maloney, J. V., Jr.; Elam, J. O.; Handford, S. W.; Balla, G. A.; Eastwood, D. W.; Brown, E. S., and Ten Pas, R. H.: "Importance of Negative Pressure Phase in Mechanical Respirators," *J.A.M.A.*, 152:212, 1953.

4 Hamilton, W. F.; Riley, R. L.; Attyah, A. M.; Cournand, A.; Powell, D. M.; Himmelstein, A.; Noble, R. P.; Remington, J. W.; Richards, D. W., Jr.; Wheeler, N. C., and Withan, A. C.: "Comparison of the Fick and Dye Injection Methods of Measuring Cardiac Output in Man," *Am. J. Physiol.*, Vol:153, 1948.

5 Gilford, S. R.; Gregg, D. E.; Shadle, O. W.; Ferguson, T. B., and Marzetta, L. A.: "Improved Cuvette Densitometer for Cardiac Output Determinations by Dye-dilution Method," *Rev. Scientific Instruments*, 24:696, 1953.

6 Theilen, E. O.; Gregg, D. E.; Paul, M. H., and Gilford, S. R.: "Determination of Cardiac Output with Cuvette Densitometer for Determination of Cardiac Output in Presence of Reduced Arterial Oxygen Saturation," *Circulation Research*, 1:200, 1953.

7 Stewart, G. N.: *J. Physiol.*, 22:159, 1897.

8 Gregg, D. E.: Personal communications.

9 Feinsilver, O.: "Circulatory Changes Associated with IPPB," Abstracts Nat. Tuberc. Assoc., Kansas City, Mo., May 1957.

10 Weber, E. F.: "Ueber ein Verfahren, den Krieslauf des Blutes und die Function des Herzens willkürlich zu unterbrechen," *Arch. f. Anat. Physiol. u. wissenach. Med.*, p. 88, 1851.

11 Gorlin, R.; Knowles, J. H., and Storey, C. F.: "The Valsalva Maneuver as a Test of Cardiac Function," *Amer. J. of Med.*, 1957.

12 Goldberg, H.; Elisberg, E. I., and Katz, L. M.: "The Effects of the Valsalva-like Maneuver Upon the Circulation in Normal Individuals and Patients with Mitral Stenosis," *Circulation*, 5:38, 1952.

13 Knowles, J. H.; Gorlin, R., and Storey, C. F.: "Clinical Test for Pulmonary Congestion with Use of the Valsalva Maneuver," *J.A.M.A.*, 160:44, 1956.

14 Hamilton, W. F.; Woodbury, R. A., and Harper, H. T.: "Arterial, Cerebrospinal, and Venous Pressures in Man During Cough and Strain," *J. Am. Physiol.*, 141:42, 1944.

15 Lawson, H. D.; Bloomfield, R. A., and Cournand, A.: "The Influence of Respiration on the Circulation in Man with Special Reference to Pressures in the Right

Auricle, Right Ventricle, Femoral Artery and Peripheral Veins," *Am. J. Med.*, 1:315, 1946.

16 Maloney, J. V., Jr., and Whittenberger, J. L.: "Direct Pulmonary Effects of Pressure Breathing," *Federation Proc.*, 10:88, 1951.

17 Seevers, M. H., and Waters, R. M.: "Respiratory and Circulatory Changes During Spinal Anesthesia," *J.A.M.A.*, 99:961, 1932.

18 Beecher, H. K.; Bennett, H. S., and Bassett, D. L.: "Circulatory Effects of Increased Pressure in Airway," *Anesthesiology*, 4:612, 1943.

19 Carr, D. T., and Essex, H. E.: "Certain Effects of Positive Pressure Respiration on Circulatory and Respiratory Systems," *Am. Heart Journal*, 31:53, 1946.

20 Sharpey-Schafer, E. P.: "The Peripheral Circulation in Circulatory Failure," *Brit. Med. Bul.*, 8:331, 1952.

21 Cathcart, R. T.; Nealon, T. F., Jr.; Fraimow, W.; Hampton, L. J., and Gibbon, J. H., Jr.: "Cardiac Output under Anesthesia," *Ann. Surg.*, In Press.

22 Sarnoff, S. J.; Maloney, J. V., Jr., and Whittenberger, J. L.: "Electrophrenic Respiration: V. Effect on the Circulation of Electrophrenic Respiration and Positive Pressure Breathing During the Respiratory Paralysis of High Spinal Anesthesia," *Ann. Surg.*, 132:921, 1950.

23 Gordon, A. S.; Frye, C. W., and Langston, H. T.: "The Cardiorespiratory Dynamics in the Open and Closed Chest," *J. Thor. Surg.*, 32:431, 1956.

The Use of Cardiopulmonary Bypass in Cardiac Surgery

With the advent of extracorporeal circulation, new vistas have been opened for the surgical correction of most of the congenital and many of the acquired intracardiac lesions.

Intracardiac defects of congenital origin were the first to be attacked by the surgeon with this technique. Many are accepted as being best repaired by open cardiotomy. These include ventricular septal defects and Tetralogy of Fallot. In interatrial septal defects and pulmonary stenosis, however, there is still some controversy as to the best technique.

Ventricular Septal Defect

The progressive course of the high membranous defect, without correction, is well known. Originally, pulmonary hypertension is produced by the left to right shunt. Eventually, however, pulmonary arteriolosclerosis ensues, which tends to perpetuate the pulmonary hypertension. This leads to a decrease in the left to right shunt, and eventually, to its reversal.

Patients with moderate pulmonary hypertension are good candidates for intracardiac surgery. Those without pulmonary hypertension can be kept under close surveillance without harm. There is still a question as to whether patients with severe pulmonary hypertension, with little or no shunt, should be operated upon. In these, the risk is high, and it is not yet determined whether closure of the defect will be followed by a reversal of the pulmonary arteriolar pathology.

Tetralogy of Fallot

There is some controversy as to which patient with Tetralogy of Fallot should be operated upon using an open technique and which with a shunt procedure. Because open heart surgery under the age of twelve to eighteen months is fraught with a high risk, infants in this bracket who have become symptomatic, are best treated with a shunt. In those patients who are doing well, surgery should be postponed until the optimal age of three to five years. At that time the lesion is best completely corrected using extracorporeal bypass. Originally, the risk for the complete correction of this lesion was high. However, the realization of the importance of an adequate right ventricular outflow tract, and the development of the technique of inserting a prosthetic outflow patch, have diminished the risk considerably. In those patients in whom an outflow tract can be restored without a prosthesis, complete correction is possible. Those requiring an outflow tract patch must be observed to determine the long-term effect upon the heart of both the prosthesis and the creation of a pulmonary insufficiency.

Atrioseptal Defects

There are those clinics in which these lesions are repaired using closed or semi-closed, blind techniques. The difficulty with complicated lesions

and the uncertainty of a complete repair, precludes the acceptance of this approach. Several clinics have effectively utilized hypothermia, which emphasized the advantage of repairing these lesions under vision. However, it has the disadvantage of imposing a time limit upon the surgeon. The complicated lesions, including transposed pulmonary veins, transposed inferior vena cava, transposed superior vena cava and high septum secundum defects obviously tax the ability of the surgeon when a time limit is imposed. It goes without saying that the more complicated ostium primum defects and atrioventricular canal cannot be repaired by this technique.

We prefer extracorporeal bypass with the pump oxygenator for the repair of atrioseptal defects. Many complicated lesions could not have been corrected under a hypothermic technique. These included three high septum secundum defects associated with transposed upper and middle lobe pulmonary veins; two transposed inferior venae cavae; several with multiple defects; one ostium primum and one in which a pulmonary valvular stenosis was associated with transposed pulmonary veins without associated atrioseptal defect. In all, with extracorporeal circulation, a complete repair was effected using an accurate, meticulous technique. To eliminate unnecessary periods of cardiopulmonary bypass, the atria were first explored digitally at which time the lesions were assessed and the technique of repair decided upon. This maneuver lead to an expeditious, carefully planned, and accurate repair.

Pulmonary Stenosis

There has been controversy as to whether the safest technique for the repair of this lesion is under hypothermia, or extracorporeal bypass. There is no doubt however, but that the lesion is best repaired under direct vision. Usually a stenotic pulmonary valve is tricuspid. The cusps are thickened and the commissures fused. In some cases the valve is bicuspid. Invariably, however, the stenotic leaflets are supported by either two or three commissures. Under vision, the stenotic valve is opened accurately and meticulously by incising the fused commissures to the annulus of the pulmonary artery. In addition, a finger should be inserted into the ventricle to explore the outflow tract for an infundibular stenosis or a septal defect.

Because of our familiarity with extracorporeal bypass we have preferred it to hypothermia for the repair of this lesion. We have felt more secure in the knowledge that the pump was present to support the circulation in the event of a complicating defect or cardiac arrhythmia. We have not regretted choosing this technique.

Acquired Lesions

Mitral Insufficiency

Whereas stenotic lesions of the mitral valve are best corrected, with minimal risk, by a closed technique, regurgitant lesions of this valve could not be attacked prior to the advent of open heart surgery. The regurgitant jet occurs at the posterior commissure and lends itself to a

direct attack through a right transthoracic approach. This permits the surgeon to cannulate the heart, and enter the left atrium with relative ease.

Under extracorporeal bypass the left atrium is opened and the lesion assessed. In some cases, suturing the annulus enables the leaflets to coapt more accurately. In others, in which there is a deficiency of valve substance, plastic materials can be added to the valve leaflets. For those patients in which the valve is deformed to point of nbn-correctability, its complete replacement by a plastic prosthesis will soon be possible.

Aortic Stenosis And Insufficiency

Previously, aortic valvular lesions were corrected using closed techniques. With the advent of extracorporeal circulation, congenital aortic stenosis was successfully corrected under vision, accurately and meticulously, with a relatively low risk. The approach was then applied to acquired lesions of the aortic valve. All too soon the difference in the pathology was recognized. Whereas the congenital lesions presented thickened but pliable leaflets without calcification, the acquired lesions were frequently heavily calcified, with destruction of both the valve leaflets and commissures. Consequently, although these lesions are best corrected under direct vision, there are many valves in which the pathology is not correctable. These cases must await the development of a dependable plastic valvular prosthesis.

Regurgitant lesions of the aortic valve, too, are best corrected under vision. The technique for the correction varies, depending upon the existing pathology. In most cases, the regurgitation can be corrected by converting the valve to a bicuspid one. The risk of this type of procedure is still high. It would seem that here, too, complete correction of many of these valves must await the development of a good plastic prosthesis.

A scant few years ago cardiac surgery was unheard of. Over the past 15 years many lesions were successfully attacked using blind, closed techniques. It was apparent that if the interior of the heart, itself, were to be inspected and repaired. Only under direct vision can the various lesions be repaired safely and accurately. In addition, the presence of a dependable cardiac pump to support the circulation in the event of a catastrophe, lends added safety to the patient and confidence to the surgeon.

ALVIN A. BAKST, M.D., F.C.C.P.*
Brooklyn, New York

*Jewish Hospital of Brooklyn

ELECTROCARDIOGRAM OF THE MONTH

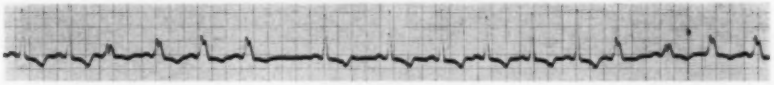
Left Ventricular Hypertrophy, Atrial Extrasystoles and Intermittent Bundle Branch Block

This tracing (Lead I) was obtained from a 42 year old man with essential hypertension. No digitalis had been given.

The first two beats have the configuration typical of left ventricular hypertrophy. Then an atrial extrasystole appears and it is aberrantly conducted within the ventricles. The following three sinus beats are similarly conducted. The T wave of the third aberrant sinus beat is distorted by the P wave of an atrial extrasystole which is blocked. Therefore, the conduction system has time to recover and the following sinus beat has again the configuration of left ventricular hypertrophy as noted in the first two beats of the tracing.

Following this series of events, a blocked extrasystole is again seen in the T wave of the seventh QRS complex. Five regular sinus beats follow and an artial extrasystole with aberrant intra-ventricular conduction appears. The next three sinus beats also are aberrantly conducted.

Thus the tracing shows a pattern of left ventricular hypertrophy, atrial extrasystoles which are partly blocked and partly aberrantly conducted and intermittent bundle branch block.



When the atrial extrasystoles are conducted to the ventricles, the left bundle branch is still refractory from the preceding sinus beat; therefore, conduction takes place over the right bundle branch. When the next sinus impulse arrives, it also traverses the right bundle branch which had conducted earlier than the left and therefore recovers earlier. Thus the pattern of conduction to the ventricles is the same as for the atrial extrasystole. Only when a blocked extrasystole leads to a longer recovery phase does the bundle branch block disappear.

DAVID SCHERF, M.D., F.C.C.P.
New York, New York

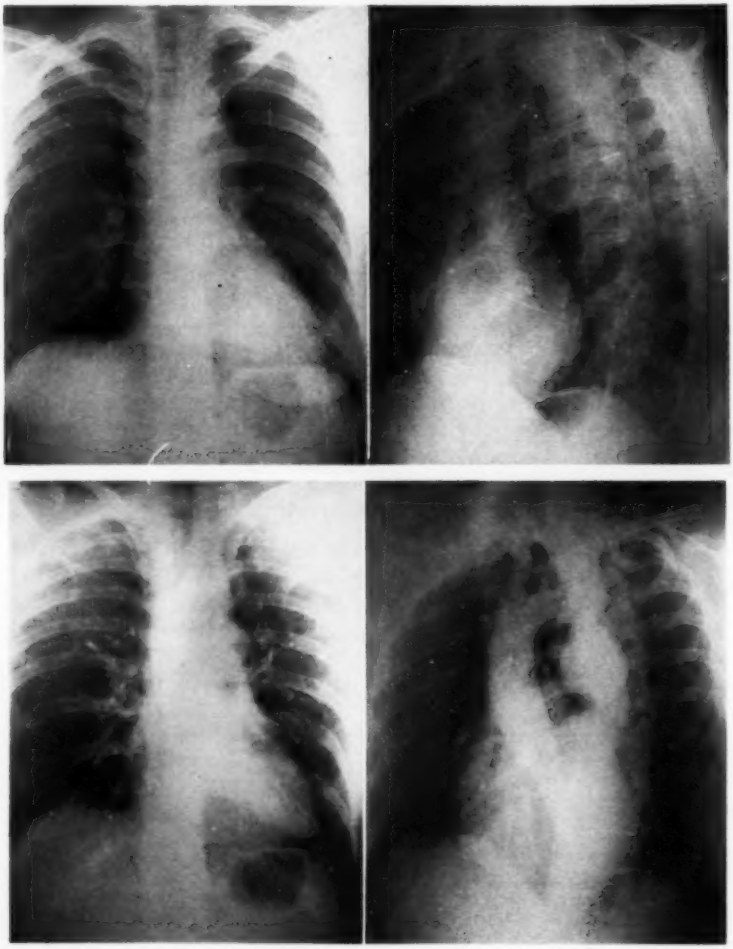
The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

Clinical Information

A white woman, aged 30, was a known cardiac all her life. She had a loud systolic murmur at the base of the heart, transmitted to the vessels of the neck, and a loud second aortic. X-ray examinations in the past have been interpreted as cardiac enlargement with hypervascularization of the lung fields. No decompensation. During pregnancy, nine years ago, had elevation of blood pressure and some arhythmia, went through pregnancy without difficulty and blood pressure returned to normal.

Seven months ago became acutely ill with fever, chilliness and general aching. No response to salicylites. Blood culture at first negative, subsequently positive for streptococcus viridans. She received large doses of penicillin for five weeks and recovered. No source for the infec-



tion found. X-ray examination revealed a mass in the left hilar region which has persisted for the past seven months. The acute episode was diagnosed as acute bacterial endocarditis. Mantoux positive during the acute episode.

The cardiac condition was thought by some to be a congenital anomaly and by others as an aortic lesion due to rheumatic fever. Because of the positive Mantoux, the mass at the left hilum was thought to be a tuberculous node. A suggestion was made of an aneurysmal dilatation resulting from the weakening of the wall of the vessels by the bacterial endocarditis, or endarteritis.

The x-ray examination shows a mass in the region of the left hilum, between the arch of the aorta and the base of the heart. In the LOA projection, there is a large pear-shaped mass in the mediastinum compressing the left main bronchus.

Angiocardiographic examination reveals a segmental dilatation in the proximal descending aorta. The left internal mammary artery is dilated. There is a slight constriction in the aorta proximal to the proximal to the segmental dilatation.

The segmental dilatation may be due to the suggestion indicated above. My impression is that it is a mild coarctation, with a post-stenotic dilatation. A review of all the films discloses irregularities to the lower margins of several of the ribs with notching caused by collaterals.

HENRY K. TAYLOR, M.D., F.C.C.P.
New York, New York

Case Report Section

The Co-Existence of Rheumatic Heart Disease and Myocardial Infarction*

CHARLES W. PFISTER, M.D., F.C.C.P.,** SAMUEL G. PLICE, M.D.† and JOAN DODSWORTH, M.D.††
Chicago, Illinois

When a patient with rheumatic heart disease presents new symptomatology, one would like to explain the episode on the basis of known lesions. The thought of unrelated, or concommitant, etiology is often overlooked. An interesting case recently encountered illustrates the fallacy of such a diagnostic approach and occasioned the study of a post-mortem series. The cases selected for review were classified on the basis of the criteria of heart disease according to the standards of the American Heart Association.[13]

Case Report: This 52 year old white woman (Case No. 43802) was admitted to the hospital February 23, 1949, complaining of oppressive, constricting substernal pain with nausea. The blood pressure was 170/70. Past history revealed rheumatic fever in childhood with cardiac symptomatology for several years. Electrocardiograms were diagnostic of anterior wall infarction and underwent serial changes. She responded to treatment and was discharged March 10, 1949, with a final diagnosis of acute myocardial infarction complicating rheumatic heart disease. After a short period of unsatisfactory progress at home, she was re-admitted because of continuing substernal distress. Dyspnea, orthopnea, basal rales, gallop rhythm, and peripheral edema were present. Blood pressure was 140/100. During hospitalization her rhythm changed to auricular fibrillation but she was discharged April 16, re-compensated. She remained relatively well until August, 1951, when the sudden onset of severe pain in the right leg occasioned re-hospitalization. The blood pressure was 210/110, and auricular fibrillation was present. There was absence of the right femoral pulse with cyanosis and coldness of the leg. Diagnosis of right popliteal artery embolism was made. She expired within a few days thereafter.

Anatomic diagnoses: (1) deforming mitral endocarditis with stenosis; (2) parietal aneurysm of the left ventricle due to coronary occlusion, ancient, with recent thrombosis of the aneurysmal lining; and, (3) embolic occlusion of the right femoral artery with extension into right common iliac artery.

Comment

The sequence of events in this patient with rheumatic heart disease and auricular fibrillation could have been attributed to embolization, pulmonary edema, or simply, rheumatic heart disease; but, in reality, were due to the sequelae of acute coronary thrombosis with myocardial infarction. The co-existence of rheumatic endocardial lesions and arteriosclerosis of the great vessels was recognized as early as 1899,[2] and coronary arteritis has been described in rheumatic fever,[4] infection,[5] and hyperergy.[11] Sudden death during active rheumatic fever has been described,[7,9,10] even in infancy.[14]

Post-mortem studies have revealed a significant incidence of combined rheumatic and arteriosclerotic heart disease but, clinically, the dual etiology is rarely diagnosed.[12] A completely correct ante-mortem diagnosis was made in only 21 per cent of the cases in which the diseases were co-existent.[1]

A thorough search through the available literature emphasizes the fact that the true incidence of rheumatic valvular disease has not been clinically recognized,[1] and even pathologically, it may be difficult.[3,4,8,9,9]

Our material consists of 1044 cases listed as rheumatic heart disease from the Department of Pathology of a large charity hospital in the middlewest. In this series there 952 cases of pure rheumatic heart disease, and 92 cases which were combined with coronary heart disease. Figure 1 shows the incidence by decades and emphasizes that myocardial infarction is common in younger victims of rheumatic heart disease.

*From Cook County Hospital and Loretto Hospital.
**Assistant Clinical Professor, Stritch School of Medicine.
†Clinical Professor, Stritch School of Medicine.
††Associate, Stritch School of Medicine.

In the younger age group of patients with coronary thrombosis, there were several interesting pathological combinations which seem to indicate that rheumatic changes increase the likelihood of a coronary accident—one instance of occlusion of the coronary orifice by a vegetation on the aortic valve; one embolic occlusion of a coronary artery; and, one obliteration of a coronary artery by a dense pericardial plaque were found.

All degrees of rheumatic valvular involvement were encountered in the 1044 cases, and 8.0 per cent showed significant coronary vascular disease.

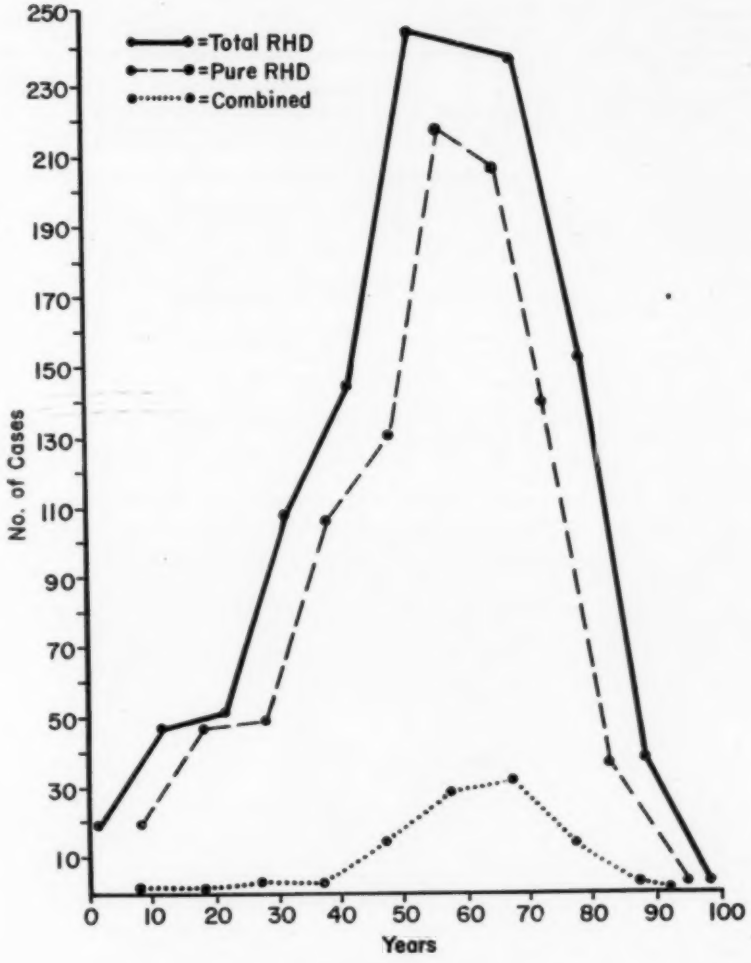


FIGURE 1

Discussion

That coronary arteritis or arteriolitis is sometimes found in severe rheumatic carditis cannot be doubted, and it could be a factor in the progressive downhill course of some cases.

Predisposition of patients with rheumatic heart disease to coronary thrombosis has been denied,[1] and yet, the end result of frequent arteritis has been described as indistinguishable from arteriosclerosis.[7,9] Surely therefore, such lesions should be expected to accelerate, enhance, or at least predispose to the location of atherosclerotic change. Local factors in the arterial wall are being stressed as at least part of the etiology of atherosclerosis. A history of rheumatic fever has been considered an adverse factor in the prognosis of coronary thrombosis.[15]

Coronary thrombosis occurs in an estimated 5 per cent of adult individuals,[16,17] but in our series, coronary thrombosis or myocardial infarction occurred in 8.0 per cent. This emphasizes that the lesions do co-exist. The possibility of acute myocardial infarction in a patient with rheumatic heart disease should be kept in mind because extensive rheumatic pathology may actually increase the likelihood of an acute coronary incident, especially in the young age group.

REFERENCES

1 Gardner, F. E., and White, P. D.: "Coronary Occlusion and Myocardial Infarction Associated with Chronic Rheumatic Heart Disease," *Ann. Int. Med.* 31:1003, 1949.

2 Huchard, H.: "Traite Clinique des Maladies Due Coeur et de L'aorte," *Vol I Paris, Doin,* 1899.

3 Levine, S., and Kauvar, A. J.: "The Association of Angina Pectoris or Coronary Thrombosis with Mitral Stenosis," *J. Mt. Sinai Hosp.* 8:754, 1941-1942.

4 Karsner, H. T., and Bayless, F.: "Coronary Arteritis in Rheumatic Fever," *Am. Heart J.* 9:557, 1934.

5 Perry, C. G.: "The Main Branches of the Coronary Arteries in Acute Rheumatic Carditis," *Quart. J. Med.* 23:241, 1929-1930.

6 Laws, C. L., and Levine, S. A.: "Clinical Notes on Rheumatic Heart Disease with Special Reference to the Cause of Death," *Am. J. Med. Sc.* 186:833, 1933.

7 Griffith, G. C., and Huntington, R. W.: "Sudden Death in Rheumatic Fever," *Ann. Int. Med.* 25:283, 1946.

8 French, A. J., and Dock, W.: "Fatal Coronary Arteriosclerosis in Young Soldiers," *J.A.M.A.* 124:1233, 1944.

9 Saphir, O., and Gore, I.: "Evidence for an Inflammatory Basis of Coronary Arteriosclerosis in the Young," *Arch. Path.* 49:418, 1950.

10 Gelin, G., and Harriague, G.: "Coronary Attack During Mitral Stenosis," *Presse Medicale* 58:992, 1950.

11 Swift, H. F., and Hitchcock, C. H.: "Rheumatic Fever as a Manifestation of Hypersensitiveness, (allergy or hyperergy) to Streptococci," *Tr. A. Am. Phys.* 43:192, 1928.

12 Chasnoff, J., and Silver, A.: "The Co-existence of Rheumatic and Arteriosclerotic Heart Disease in Patients Over the Age of 40 Years," *Am. Heart J.* 42:809, 1951.

13 American Heart Association, New York, New York: *Heart Disease,* 1931.

14 Martelle, R. R.: "Coronary Thrombosis in a Five Month Old Infant," *J. Ped.* 46:322, 1949.

15 Billings, F. T., Jr.; Kalstone, B. M.; Spencer, J. L.; Ball, C. O., and Meneely, G. R.: "Prognosis of Acute Myocardial Infarction," *Am. J. Med.* 7:356, 1949.

16 American Heart Association: *Cardiovascular Disease in the U. S., Facts and Figures,* March, 1958.

17 U. S. Dept. of Health, Education and Welfare, U. S. Public Health Service, Wash, D. C.: *Vital Statistics for Illinois and State Economic Areas, 1955,* (State of Illinois, Dept. of Public Health, Bureau of Statistics), 1958.

Localized Obstructive Emphysema Produced by an Extrabronchial Lesion

CARL OSHRAIN, M.D.* AND COLEMAN H. ROSENBERG, M.D.*
Brooklyn, New York

The purpose of this paper is to report a case of localized obstructive emphysema caused by extrabronchial lymph-nodular giant follicular lymphoblastoma. No comparable case has been found in the literature of the past 30 years. In addition, there are very few reports of localized obstructive emphysema being produced by lesions of any nature that are entirely extrabronchial.[1-4]

Case Report

J. P. (J. H. No. 415778), a 17 year old white student, was admitted to the hospital July 11, 1957 after demonstration of a left hilar mass on a routine chest film by a mobile unit. The mass was not present one year previously on a similar chest film.

Except for occasional right parasternal pain on deep inspiration for the past year, he had been essentially asymptomatic. A cold one year prior to admission, followed by three weeks of non-productive cough, had responded to non-specific medication. He had smoked one pack of cigarettes per day for the past year and one-half.

Past history and family history were irrelevant.

Physical examination revealed him to be well developed, well nourished and in no distress. Multiple small, non-tender, moveable nodes were palpated in both cervical, axillary and inguinal regions. There was no other significant physical finding.

Laboratory Findings

Peripheral blood, bone marrow, heterophile agglutination and urinalysis were normal. Gastric washings for acid-fast bacilli were repeatedly negative. Biopsy of an axillary lymph node revealed only "fibrosis producing distortion of the nodal architecture; no tumor cells seen."

The chest film showed a well circumscribed, homogeneously dense, lobulated 5 cm. shadow at the left hilus, and emphysema at the left base (Fig. 1). At fluoroscopy, the mass neither pulsated, changed in size on Valsalva maneuver, nor moved on swallowing. There was no relation to the esophagus, and no mediastinal shift was noted. Tomograms suggested relationship of the mass to the left main bronchus (Fig. 2). Bronchoscopy revealed no abnormality of the major bronchi or their proximal branches, all of which were visualized. Bronchography showed a persistent filling defect in the proximal portion of the antero-medial segmental bronchus of the left lower lobe, contiguous with the hilar mass (Fig. 3). This was interpreted as the endobronchial component of a bronchial adenoma, and the cause of the left lower lobe emphysema.

*From the Departments of Medicine and Radiology, Jewish Hospital of Brooklyn.

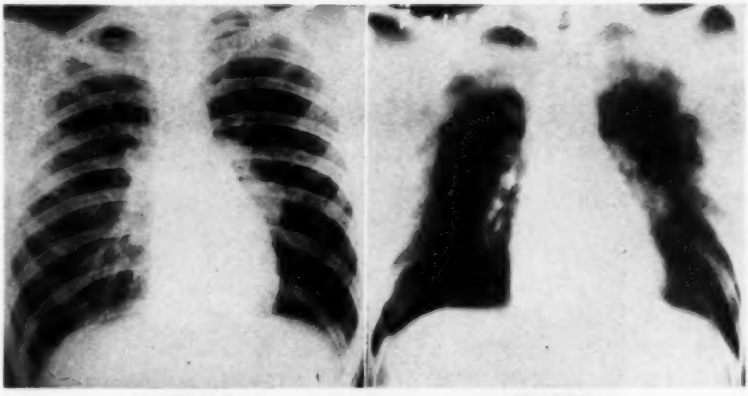


FIGURE 1 FIGURE 2

FIGURE 1. Chest roentgenogram. A well circumscribed 5 cm. shadow at the left hilum, and emphysema at the left base are demonstrated. FIGURE 2. Tomogram. Relationship of the mass to the left main bronchus is suggested.

Left lower lobectomy was performed, the tumor mass was removed in its entirety. The pathologic report was "Giant follicular lymphoblastoma." No endobronchial component of the tumor could be found, the entire tumor being contained in a parabronchial lymph node (Fig. 4). Areas of atelectasis were not found.

Because the tumor had been removed in toto, no further therapy was given. Recovery was uneventful and he is being followed in the tumor clinic.

Discussion

Peribronchial tuberculous adenopathy, frequently associated with edema of the bronchial mucosa, has been reported as a cause of regional obstructive emphysema.[6,13,14] Aberrant vessels, aortic aneurysms and enlarged hearts are also mentioned as causes of bronchial compression and resultant localized obstructive emphysema.[5,8,12]

There are innumerable reports of:

1. Obstruction and atelectasis produced by extrabronchial lesions; and
2. Obstruction and emphysema produced by intrabronchial lesions, but aside from the few reports mentioned above, regional emphysema involving a lobe or segment of a lobe, which is not associated with aspiration of a foreign body,[7] carcinoma,[3] adenoma,[9] or tenacious mucous,[1] has received little attion.

The causal mechanism in regional obstructive emphysema is well known through the bronchoscopic studies of Jackson and his colleagues.[7] They observed that bronchi expand and lengthen during inspiration, and contract and shorten during expiration. Thus, they pointed out, thick viscid inflammatory exudate, as well as foreign bodies, carcinomas, and adenomas can cause bronchial obstruction, and produce either atelectasis or emphysema. If obstruction is complete, regional atelectasis occurs (stop-valve mechanism); if incomplete, inflow of air is permitted and outflow restricted, resulting in regional emphysema.

There would appear to be no logical reason why an exobronchial lesion might not cause partial obstruction and localized emphysema prior to atelectasis. Either this period is brief and goes unrecognized, or the emphysema occurs only where one of the lesser bronchi, devoid of hilar structural support, is compressed. Even in cases of bronchial adenoma, where the phenomenon of obstructive emphysema is frequently observed, the great majority of cases present only atelectasis radiographically.[9] Since

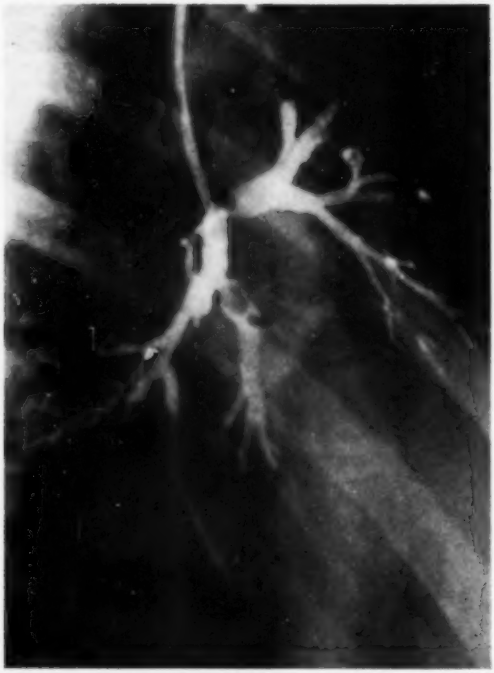


FIGURE 3. Bronchogram. A persistent filling defect in the proximal portion of the antero-medial segmental bronchus of the left lower lobe, contiguous with the hilar mass is demonstrated.

symptoms are probably more pronounced in the presence of atelectasis, discovery of the emphysematous stage may only be by chance. It seems likely, therefore, that cases of bronchial obstruction which show atelectasis would have at some time earlier demonstrated emphysema, as this case did; and just as likely that this case would later have shown atelectasis when obstruction was more complete.

Lymphomas, associated with atelectasis either by lymph nodular compression or direct bronchial invasion, are well known.[2,4,10,11] Obstructive emphysema has not to our knowledge received prior mention.

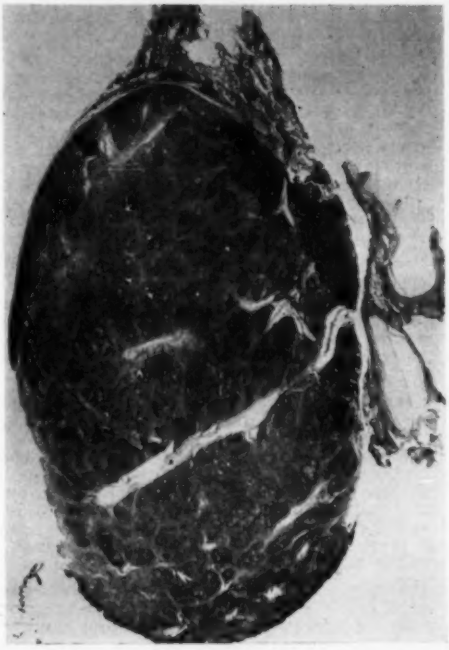


FIGURE 4. Section through the lymph node containing lymphoma and the bronchus which was compressed by the tumor.

REFERENCES

1 Caffey, J.: "Regional Obstructive Pulmonary Emphysema in Infants and Children," *Am. J. Dis. Child.;* 60: 586, 1940.

2 Gall, E. H., and Mallory, T. B.: "Malignant Lymphoma; Clinico-Pathologic Survey of 618 Cases," *Am. J. Path.;* 18: 381, 1942.

3 Golden, R.: "Effect of Bronchostenosis Upon Roentgen-ray Shadows in Carcinoma of Bronchus," *Am. J. Roentgenol.;* 13: 21, 1925.

4 Heathy, C. A.: "Localized Pulmonary Hodgkin's Disease; Bronchoscopic Aspects; Case Report," *Ann. Otol. Rhin. and Laryng.;* 59: 705, 1950.

5 Holinger, P., and Andrews, A. H., Jr.: "Bronchiial Obstruction; Signs, Symptoms and Diagnosis," *Am. J. Surg.;* 54: 193, 1941.

6 Holmes, G. W.: "Roentgen Diagnosis of Obstructing Bronchial Lesions," *Northwest Med.;* 41: 370, 1942.

7 Jackson, C., Spencer, W. H., and Manges, W. F.: "Diagnosis and Localization of Non-Opaque Foreign Bodies in the Bronchi," *Am. J. Roentgenol.;* 7: 277, 1920.

8 Morse, H. R., and Gladding, S.: "Bronchial Obstruction Due to Misplaced Left Pulmonary Artery," *A.M.A. Am. J. Dis. Child.;* 89: 351, 1955.

9 Peterson, H. O.: "Benign Adenoma of Bronchus," *Am. J. Roentgenol.;* 36: 836, 1936.

10 Rubin, E. H.: "Diseases of Chest," W. B. Saunders Co., Phila., pg. 503, 1948.

11 Schinz, H. R., Baensch, W. E., Friedl, E., and Uehlinger, E. "Roentgen-Diagnostics," Grune and Stratton, N. Y., Vol. III, 1951.

12 Thompson, J., and Forfar, J. C.: "Regional Obstructive Emphysema in Infancy," *Arch. of Dis. Child.;* April, 33: 97, 1958.

13 VanAllen, C. M.: "Obstructive Pulmonary Emphysema, etc." *S. G. and O.;* 55: 308, 1932.

14 Wessler, H., and Jaches, L.: "Clinical Roentgenology of Diseases of the Chest," The Southworth Co., Troy, N. Y., pg. 50, 1923.

The President's Page

THE PHYSICIAN AND THE GREAT BOOKS

At the beginning of the modern age, when men first began to sense the immense power that lay locked up in the knowledge of the physical world, a geometrician asked Samuel Johnson, of dictionary fame, why he thought men should continue to waste their time studying the classics. "Because, sir" answered Johnson, "a man is a geometrician by accident; he is a moralist by nature." The observation is a valid one. It is only to say that a human being is a man first, that he is only a geometrician, or a scientist or a physician, secondarily.

The distinction in theory is a simple one, however much it has been obscured by varied thinking on the part of the social scientists. A science can only tell us what has been, what is, or what is to be; it is a description of existence. But no scientist, as *scientist*, can tell us what *ought* to be. "Ought" is an expression of preference; it implies that alternatives are being measured in terms of some pre-existing standard of desirability. As scientists we describe and predict, but we are never purely, or even mostly, scientists. We are primarily human beings, which means that we live primarily in terms of ought. Every man values and judges incessantly. Even scientists do it, in spite of themselves. And for every purely scientific statement the physician makes in the course of a day, he will make five statements that are not scientific, that contain, however obscurely, an expression of preference, a value judgment.

There is nothing wicked about this, unless one wishes to blame human beings for their humanness. But there is an obligation upon us, perhaps, to recognize a value judgment when it is made, and to make sure that we really believe in the kind of values we assume. If we are not aware of our basic values, if we do not recognize value judgments for what they are, our science is at the mercy of the most irrational forces imaginable.

To take an obvious example: The profoundest commitment most of us have is to our children. And yet, although this is the one job above all others we would like to do well, our science is of only subordinate use to us. And we are blessed with innumerable books on the subject, and they are of little value either, at least until we have answered the fundamental questions for ourselves. The only possible response to the question, "How shall I bring up my child?" is another question, "What kind of child do you want?" And anybody who brings up a child, or who writes a book about it, has to answer the fundamental question, in one way or another. The hazard is that we can answer the question, by our behavior at any rate, without ever really thinking about it, without fully recognizing its existence.

Which brings us to the physician's proper relationship to the great books. If there is one characteristic which can be attributed to writers as a subspecies of *homo-sapiens* it is their willingness to confront such fundamental questions. "What is man that thou art mindful of him," the Psalmist asked a good many years ago. We must all answer this question in our daily behavior, but our answers are generally thoughtless ones. The writer has the peculiar capacity to sit down in front of such a vast problem and contemplate it.

There isn't any answer to such a question of course, and great books do not give us one. Instead they give us answers, many of them, to the same question. Which shouldn't surprise us, since writers, while they belong to the genus man, are also individual men, living lives no one of which is quite like another. Nor can any of them give us *our* answer, since our life in turn has not been his. But in this difference, paradoxically, lies their great value. In the first place, they invite us to consider the big questions of value. They propose answers which are partially true for us, and which make us dissatisfied with the thoughtless, complacent, superficial answers upon which we have heretofore depended, knowingly or not. No man of the twentieth century, for instance, can whole-heartedly espouse Shakespeare's exalted conception of man; he lived at a different time, and perhaps we know too much about man. But he can make us permanently dissatisfied with "child authorities" and suspicious of the easy definitions of those who propose to reduce man to what they can measure.

And this is an invitation, finally, to formulate our own answers to large questions. What the great books can finally teach us is to know ourselves, to make us conscious of the meaning, in terms of values, of our own experience. With their help, we can learn to formulate our own answer to the question, "What kind of man or woman do you want your child to mature into." And our own answer is certain to be better, for us, than anybody else's.

Seymour M. Farber

26th ANNUAL MEETING OF THE COLLEGE

The 26th Annual Meeting of the American College of Chest Physicians will be held at the Saxony Hotel, Miami Beach, Florida, June 8 - 12, 1960. A number of excellent nearby oceanfront hotels will be available to house the attending members. Please refer to page XXVII for a convenient form for your hotel reservations. It is suggested that members planning to attend the annual meeting submit their requests for reservations as early as possible in order to be assured of obtaining the type of accommodations desired.

Dr. Thomas W. Mattingly, Washington, D.C., and Dr. R. Drew Miller, Rochester, Minnesota, co-chairmen of the scientific program committee, report that an excellent program is being organized. In addition to formal presentations on cardiovascular and pulmonary subjects, there will be the popular round table luncheon discussions and fireside conferences. A program of new films on diseases of the chest is being arranged by Dr. Paul H. Holinger and his Committee on Motion Pictures. A first prize certificate will be awarded for the best film presented in the program and some honorable mention certificates may also be presented, depending upon the decision of the judging committee. A series of informative postgraduate seminars will be given on Wednesday, June 8.

PROCEEDINGS OF THE BOARD OF REGENTS

Two meetings of the Board of Regents of the College were held during the fall of 1959, on October 14 in Albuquerque, New Mexico, in connection with the Homecoming Meeting, and in Dallas, Texas on November 29, during the interim session of the College. Dr. Arthur M. Olsen, Rochester, Minnesota, chairman of the Board, presided at both meetings. The following matters were discussed at the Albuquerque meeting:

The Treasurer of the College, Dr. Charles K. Petter, read the following resolution which was adopted by the Board:

WHEREAS, the activities of the College have increased over the years, and

WHEREAS, this increase in College activities has necessitated the employment of additional personnel at the executive offices in Chicago, and

WHEREAS, it has been necessary to expand the facilities occupied by the College in its building, and

WHEREAS, the cost of printing **Diseases of the Chest**, as well as all other printing and administrative costs, have increased during the past ten years, and

WHEREAS, there has not been an increase in the annual dues of the members for the past ten years, and

WHEREAS, it is essential for the proper functioning of the College to increase its present revenue in order to meet the current operating expenses,

THEREFORE BE IT RESOLVED, that effective January 1, 1960 the annual dues for members in the United States and Canada be increased from $25.00 to $35.00 per year.

The report of the Committee on College Bylaws was presented by Dr. Carl H. Gellenthien, chairman, and adopted. The proposed amendments, to be voted upon by the membership at the annual meeting in Miami Beach on June 9, are as follows:

REPORT OF THE COMMITTEE ON COLLEGE BYLAWS

Amendments to the College Bylaws will be presented to the membership for approval at the time of the open administrative session to be held in Miami Beach, Florida, in connection with the 26th Annual Meeting of the College, June 8-12, 1960. The open administrative session will be held at 2:00 p.m. on Thursday, June 9th. The amendments are as follows:

ARTICLE V, Board of Regents

Section 2: One of the members of the Board of Regents shall be elected as its Chairman, **and one as Vice-Chairman,** by a majority vote of the members of the Board of Regents present at an annual meeting. The Chairman **and Vice-Chairman** shall serve for one year and shall be eligible for re-election at each annual meeting . . . . .

Section 6: (Last sentence) The Chairman shall preside at all meetings; in his absence the **Vice-Chairman** shall preside.

Section 7: During the interim periods between meetings of the Board, the business affairs of the College shall be managed by an Executive Council composed of the President, the President-Elect, the First Vice-President, the Second Vice-President, the Treasurer, the Assistant Treasurer, the Chairman, **the Vice-Chairman,** and one elected member of the Board of Regents . . . . .

ARTICLE X, Councils and Committees

Section 4: (a) The following councils, consisting of nine members each, shall be appointed:

Council on Undergraduate Medical Education
Council on Postgraduate Medical Education
Council on Cardiovascular Research
Council on Pulmonary Research
Council on Public Health
Council on Hospitals

(b) The chairmen of all councils shall serve as ex-officio members of the Board of Regents for the purpose of reporting the activities of their councils at the meetings of the Board of Regents.

(c) All policies, programs and expenditures recommended by these councils must be approved by the Board of Regents **before becoming effective.**

Section 6: The President shall appoint such committees which may be necessary to carry out the objectives of the College. The number of members to serve on any committee shall be determined by the President. The chairmen of councils and committees may appoint sections to serve under the jurisdiction of their council or committee. Members of all committees and sections shall serve for a one-year term and may be reappointed. Committees may be discharged by the President or the Board of Regents after they have served their purpose.

Section 7: There shall also be a Committee on Nominations consisting of three Fellows of the College. One member shall be a member of the Board of Regents and he shall be elected by the members of the Board of Regents at their annual meeting. One member shall be a member of the Board of Governors and he shall be elected by the members of the Board of Governors at their annual meeting. The third member of the committee shall be a Fellow at large and he shall be appointed by the President **not later than thirty days after assuming that office. The President shall designate the chairman of the Committee on Nominations. The Committee on Nominations shall hold a meeting prior to the end of the current year for the purpose of selecting a list of nominees for the following elective offices:**

(1) President-Elect,
(2) First Vice-President,
(3) Second Vice-President,
(4) Treasurer,
(5) Assistant Treasurer,
(6) Historian,
(7) Regents whose terms expired during the current year, and
(8) Governors whose terms expired during the current year.

The names of the members of the Committee on Nominations shall be published in the official journal of the College not later than sixty days prior to the annual meeting. Any member in good standing may submit recommendations for elective offices to the Committee on Nominations. Nominations by the Committee on Nominations shall not preclude nominations from the floor at the elections of the various officers.

Carl H. Gellenthien, Chairman
S. Eugene Dalton
Samson D. Entin
Robert E. Schwartz
Henry J. Stanford

STATEMENT ON CANCER OF THE LUNG

The following statement on cancer of the lung, submitted by Dr. Seymour M. Farber, President, was approved without a dissenting vote:

The rate of increase of cancer of the lung has reached disturbing proportions. This is of serious concern to the medical profession and particularly to the chest physician. It accordingly becomes mandatory that every effort be exercised to establish the causative factors that may be responsible for lung cancer.

A tremendous amount of research is being conducted in various institutions and research centers throughout the country in an attempt to ascertain the cause of this disease. While many theories have been advanced, including the involvement of cigarette smoking, noxious industrial fumes and other respiratory irritants, it is the concensus of the Board of Regents of the American College of Chest Physicians that further work must be carried out before any single agent or agents can be definitely implicated.

We can, however, report that as the result of intensive research, new methods have been developed to assist the physician in early diagnosis of cancer of the lung. Our most important ally in dealing with cancer of the lung is the family physician who sees the patient early in the course of this disease and who makes available the necessary diagnostic techniques. Early diagnosis remains our greatest weapon in combatting cancer of the lung. A frequent check-up by your physician, which must include x-rays of the chest, is highly recommended.

Dr. Andrew L. Banyai, chairman of the Council on International Affairs, announced the establishment of 25 international committees, with 451 members serving in 65 countries and territories. The international committees will meet at the University of Vienna on August 27, 1960, at the time of the Sixth International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the College and presented under the auspices of the Government of Austria, August 27 - September 1. Dr. Karl Fellinger, Professor of Medicine at the University of Vienna, is serving as the President of the congress and Dr. Anton Sattler, Regent of the College for Austria, is Secretary General. More than 500 physicians and their families throughout the world have notified the College offices of their plans to attend the congress in Vienna and it is expected that this congress will exceed in attendance all of the previous international congresses of the College.

A number of committee reports were reviewed and those approved for publication by the Board of Regents will appear in future issues of **Diseases of the Chest.**

Dr. Edward W. Hayes, Sr., vice-chairman of the Council on Undergraduate Medical Education, reported on a conference held in Chicago on September 1, 1959, at the time of the Second World Congress on Medical Education sponsored by the World Medical Association, the American Medical Association and the Association of American Medical Colleges. The College conference was attended by members of the Council and Committee on Undergraduate Medical Education, as well as members from other countries, many of whom serve on the International Committee on Undergraduate Medical Education.

A report on the postgraduate courses presented by the College in 1959 was presented by Dr. J. Winthrop Peabody, chairman of the Council on Postgraduate Medical Education. Dr. Peabody announced that the very successful course on clinical cardiopulmonary physiolgy would be repeated in Chicago, October 24-28, 1960. The annual New York City postgraduate course will be presented during the week of November 14-18, at the Park Sheraton Hotel.

The Board of Regents expressed its appreciation to Dr. Burgess L. Gordon, chairman of the program committee, and to Dr. Roy F. Goddard, chairman of the arrangements committee, as well as to all of the members of the New Mexico Chapter of the College, for the splendid Homecoming meeting arranged in Albuquerque. A vote of thanks was also extended to the Governor of New Mexico and the Mayor of Albuquerque for their participation in the Homecoming ceremonies.

At the semi-annual meeting of the Board of Regents held in Dallas on November 29, 1959, Dr. Arthur M. Olsen, chairman, presented the following outline of the procedure for processing council and committee reports, which had been prepared for the information of all members serving on the various councils, committees and sections of the College.

1. Each council, committee and section is required to meet during the annual meetings of the College. At these meetings various projects are discussed and reports are prepared in writing.
2. The reports are turned over to one of the staff members at the meeting for typing,
   or
   The reports are sent to the College offices in Chicago after the meeting by either the chairman or secretary of the council, committee or section.
   All reports must contain a **record of attendance.**
3. The reports are processed at the administrative offices in Chicago for presentation to the Executive Council.
4. The reports, together with the recommendations of the Executive Council, are then submitted to the Board of Regents at one of its regular meetings.
5. The chairman of each council, committee and section is advised of the action taken by the Board of Regents before the reports are duplicated and mailed to the members of the councils, committee and sections, accompanied by a covering letter from the chairman.
6. The members of the councils, committees and sections are requested to write to the chairman, setting forth their comments. At this time, they are invited to submit additional recommendations which they feel the council, committee or section might undertake.
7. These recommendations are incorporated in the agendas which are prepared at the executive offices of the College for presentation at the next annual meeting of the council, committee or section. A copy of the agenda is mailed to every member of the council, committee or section in advance of the annual meeting, accompanied by a questionnaire asking whether or not they will be present for the meeting. All of this information is then forwarded to the chairman of the council, committee or section.
8. Reports approved by the Board of Regents of the College and recommended for publication will appear either in the official journal of the College, DISEASES OF THE CHEST, THE PUBLIC HEALTH COUNSELOR, or a special release on council and committee reports authorized by the Board of Regents of the College.
9. A record card system has been established at the executive offices of the College to maintain a permanent record of attendance of council, committee or section members at the annual meetings. It is therefore important that an accurate attendance record be submitted by the chairman or secretary of each council, committee and section.

A report of the Editorial Board for **Diseases of the Chest** was presented by Dr. J. Arthur Myers, chairman, in which he stated that there had been an increase of 45 papers and articles published in 1959. This is due, in part, to the reduction in type size for summaries and translations, as well as to the fact that the members of the Editorial Board have endeavored to reduce the length of manuscripts submitted for consideration. Effective January, 1960 the circulation of the journal will reach 9,000 copies monthly, in 89 countries and territories around the world, the largest circulation to date.

Dr. Burgess L. Gordon reported on the College books:

Roentgenology of the Chest, published by the Charles C. Thomas Company is enjoying a good sale. The latest report indicates that more than 1400 copies have been sold.

Benign and Malignant Tumors of the Chest, published by Grune & Stratton will be available in January, 1960. The price of the book is $14.75 and copies may be ordered through the College offices in Chicago.

Clinical Cardiopulmonary Physiology, published by Grune & Stratton, has been sold out and a completely revised edition is now being prepared. It is expected to be available in the spring of 1960. More than 500 advance orders are on hand for this new edition.

A book on modern graphic devices, roentgen technics and recording equipment in the diagnosis and surgery of heart diseases, edited by Dr. Arthur M. Master, is now in the hands of the publishers, Grune & Stratton, and will appear early in 1960.

The Texas Chapter of the College was commended by the Board of Regents for the outstanding scientific program organized for the interim meeting and the excellent arrangements made for the various functions. Dr. Robert R. Shaw served as chairman of the program committee and Dr. James O. Armstrong was in charge of arrangements.

Chapter News

MIDDLE EAST CHAPTER

Pictured above are members of the Middle East Chapter and guests who attended the annual meeting of the Chapter in Kuwait, November 19-22. At this meeting, the following officers were elected:

President	Elias Khoury, Beirut, Lebanon
Vice President	Wasif Kanaan, Amman, Jordan
Secretary	Toufic Al-Awar, Bhannes, Lebanon
Treasurer	Wagih K. Sabbagh, Beit Mery, Lebanon

COLLEGE CHAPTERS IN SPAIN

Members of the College Chapters in Spain recently held the Second National Congress of the College in Valencia. In the photograph above, the following officials appear: (Standing, left to right) Ricardo Llopis-Llorente, Valencia; Alvaro Urgoiti, La Coruña, Governor of Northwest Spain; Antonio Azpitarte, Granada, Secretary, Andalusian Chapter; Raimundo Frouchtman, Governor for Barcelona; Carmelo Gil-Turner, Bilbao, Governor for Bilbao; J. L. Alvarez Sala-Moris, President, Madrid Chapter; Camilo Rodriguez Gavilones, Las Palmas, President, Canary Islands Chapter; Conrad Xalabarder, President, Barcelona Chapter. (Seated, left to right): José Abelló, Governor for Madrid; Murray Kornfeld, Executive Director of the College; Anthony Caralps, Regent for Spain; and Francisco Coll Colomé, Treasure for Spain. More than 100 members of the College attended this meeting.

MISSOURI CHAPTER

The annual meeting of the Missouri Chapter will be held at the Statler Hotel, St. Louis, on Sunday, March 18, during the annual session of the Missouri State Medical Association. The program, beginning at noon, is as follows:

"Lung Biopsy in the Diagnosis of Diffuse Infiltrative Pulmonary Disease"
Peter A. Theodos, Philadelphia

"Diagnosis and Management of Lesions Requiring Open-heart Surgery"
Thomas Ferguson, St. Louis

"Anthoracosis — A Common Disease"
J. P. Wyatt, St. Louis

"Correlation of Pulmonary Function with Lung Marco Section in Emphysema"
Herbert C. Sweet, St. Louis

"Summary of 1960 Veterans Administration Tuberculosis Conference"
William Klein, St. Louis

"A Report on the Use of Cycloserine in Large Dosage in Salvage Cases of Tuberculosis"
Axel Gronau and Ellis S. Lipsitz, St. Louis

New Chapter Officers

COLORADO CHAPTER

President	Mordant E. Peck, Denver
Vice-President	Leroy Elrick, Denver
Secretary-Treasurer	D. Armin Fischer, Denver

FINNISH CHAPTER

President	Jorma Patiala, Helsinki
Secretary-Treasurer	Leo Kaarlo Noro, Helsinki

INDIANA CHAPTER

President	Alfred D. Dennison, Jr., Indianapolis
Vice-President	Arvine G. Popplewell, Indianapolis
Secretary-Treasurer	Frank W. Hare, Madison

KENTUCKY CHAPTER

President	Oren A. Beatty, Louisville
Vice-President	Daniel E. Mahaffey, Louisville
Secretary-Treasurer	Daniel N. Pickar, Louisville (re-elected)

NEW ENGLAND STATES CHAPTER

President	Francis M. Woods, Boston, Massachusetts
1st Vice President	Peter F. Harrington, Providence, Rhode Island
2nd Vice President	Ralph H. Adams, Wolfeboro, New Hampshire
Secretary-Treasurer	Samuel Clive Cohen, Boston, Massachusetts (re-elected)

PENNSYLVANIA CHAPTER

President	John M. Snyder, Bethlehem
Vice-President	Archibald C. Cohen, Butler
Secretary-Treasurer	Robert L. Mayock, Philadelphia (re-elected)

POTOMAC CHAPTER

President	Milton B. Kress, Baltimore
Vice-President	John W. Trenis, Washington, D. C.
Secretary-Treasurer	Joseph W. Peabody, Jr., Washington, D. C. (re-elected)

SOUTHERN CHAPTER

President	John H. Seabury, New Orleans, Louisiana
Vice-President	DeWitt C. Daughtry, Miami, Florida
1st Vice President	Henry R. Hoskins, San Antonio, Texas
2nd Vice President	Joseph W. Peabody, Jr., Washington, D. C.

THAI CHAPTER

President	Prasert Kangsadal, Dhonburi
Vice-President	Smarn Muntabhorn, Bangkok
Secretary-Treasurer	Sombun Pong-Aksara, Bangkok

VIRGINIA CHAPTER

President	Charles G. Pearson, Charlottesville
Vice-President	George E. Ewart, Richmond
Secretary-Treasurer	Cecil Cullen Smith, Catawba

Obituary

JAMES H. STYGALL

1887 - 1959

Members of the College were saddened and shocked to learn of the sudden death of Dr. James H. Stygall of Indianapolis, Indiana on October 18, 1959. He was a physician of outstanding renown in his specialty and a tireless and faithful devotee to the American College of Chest Physicians. Dr. Stygall was a member of the Board of Regents for many years and served as its chairman from 1950 to 1952. He served as President of the College in 1955-1956. A Charter Member, having been a member of the College almost from the time of its founding, he did much in his home state to create interest in the organization, as well as serving on many of the councils and committees during the years.

Dr. Stygall was born in Buffalo, New York in 1887 and graduated from the University of Buffalo College of Medicine in 1910. He was a captain in the Medical Corps of the U. S. Army during World War I.

Early in his career, Dr. Stygall showed great interest in chest diseases and from 1919-1920 he served as superintendent and medical director of Rocky Crest Sanatorium, Olean, New York. In 1921 he moved to Indiana and engaged in private practice, specializing in chest diseases. For many years he was a member of the Board of Directors of the Indiana Tuberculosis Association and served a term as its president. He had also been a trustee of the Indiana State Sanatorium for more than twenty years.

At the time of his death, Dr. Stygall was chief of staff at Flower Mission Hospital, and on the staffs of St. Vincent's Hospital, Methodist Hospital and Indiana University Medical Center in Indianapolis. He had been director of school nutrition for the city of Indianapolis for thirty-five years.

Dr. Stygall was a member of the Episcopal Church, a Knight Templar Mason and a Kiwanian. Everyone who knew him respected and admired him both professionally and as a friend.

Dr. Stygall is survived by his wife, the former Della Curry, a son, James H. Stygall, Jr. of Indianapolis, a granddaughter, and two brothers, Elmer of Buffalo, New York and Alfred J. of Ft. Myers, Florida.

Jerome V. Pace, M.D.
Governor for Indiana